9th Annual Report of the
National Institutes of Health

PROGRAM IN BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING FISCAL YEAR 1985

NIH Nutrition
Coordinating Committee

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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Prepared by
NIH Nutrition
Coordinating Committee

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
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Members and (Alternates)*	
National Cancer Institute	Peter Greenwald, M.D. (Ritva Butrum, Ph.D.)
National Heart, Lung, and Blood Institute	Nancy Ernst, M.S., R.D. (Basil M. Rifkind, M.D.)
National Institute of Dental Research	Matthew A. Kinnard, Ph.D.
National Institute of Arthritis, Diabetes, & Digestive & Kidney Diseases	Van Hubbard, M.D., Ph.D. (Donald G. Murphy, Ph.D.)
National Institute of Neurological and Communicative Disorders and Stroke	Zekin Shakhashiri, M.D.
National Institute of Allergy and Infectious Diseases	Robert Edelman, M.D. (John E. Nutter, Ph.D.)
National Institute of General Medical Sciences	Vivian Dickson (Leo von Euler, M.D.)
National Institute of Child Health and Human Development	Sumner J. Yaffe, M.D. (Thorsten Fjellstedt, Ph.D.)
National Eye Institute	Barbara Underwood, Ph.D. (Henry Fukui, Ph.D.)
National Institute of Environmental Health Sciences	Robert A. Goyer, M.D. (Wilford L. Nusser, Ph.D.)
National Institute on Aging	Evan C. Hadley, M.D. (Leonard F. Jakubczak, Ph.D.)
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*(Alternates in parenthesis)

As of September 17, 1985

NIH Liaison Representatives

Clinical Center	(vacant)
Division of Computer Research and Technology	Judy Mahaffey (Arnold Pratt, M.D.)
Division of Research Grants	John Schubert, Ph.D. (Donna Dean, Ph.D.)
National Library of Medicine	Harold A. Schoolman, M.D.
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OD, Office of Communications	Marc Stern

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Alcohol, Drug Abuse, and Mental Health Administration	Ellen Stover, Ph.D. (Peter Bridge, M.D.)
Centers for Disease Control	Frederick Trowbridge, M.D. (Gordon E. Robbins)
Food and Drug Administration	Allan Forbes, M.D. (Lynn A. Larsen, Ph.D.)
Health Resources and Services Administration	Elizabeth Brannon, M.S., R.D. (E. Ann Prendergast, R.D., M.P.H.)
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THE MEMBERSHIP OF THE NCC PROGRAM SUBCOMMITTEE

Chairman	Artemis P. Simopoulos, M.D.

Members

National Cancer Institute	Peter Greenwald, M.D.
National Heart, Lung, and Blood Institute	Nancy Ernst, M.S., R.D.
National Institute of Arthritis, Diabetes, & Digestive & Kidney Diseases	Van Hubbard, M.D., Ph.D.
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National Institute of Child Health and Human Development	Sumner J. Yaffe, M.D.
Division of Research Resources	Maria A. Mannarino, M.D.
Division of Research Services	Joseph J. Knapka, Ph.D.

THE MEMBERSHIP OF THE NCC SUBCOMMITTEE ON NUTRITION EDUCATION

Cochairperson	Joseph Knapka, Ph.D. Division of Research Services
Cochairperson and Executive Secretary	Karen Donato, M.S., R.D. Nutrition Coordinating Committee Office
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Members	
National Cancer Institute	Ritva Butrum, Ph.D. Luise Light, Ph.D.
National Heart, Lung, and Blood Institute	Marilyn Farrand, R.D.
National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases	Van Hubbard, M.D., Ph.D.
National Eye Institute	Barbara Underwood, Ph.D.
Division of Research Resources	Maria Mannarino, M.D.
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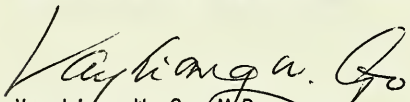
ACKNOWLEDGEMENTS

I want to pay special thanks to the Institutes' representatives to the Nutrition Coordinating Committee whose unfaltering support and interest in nutrition research has made possible the development of the report. On behalf of the Nutrition Coordinating Committee I wish to thank three members of the NCC office staff: Ms. Karen Donato for her excellent work in updating the annual report, and Dr. Thomas Vogl and Ms. Bronna Finn for their efforts in providing data for this report from the computerized data retrieval system.



Vay Liang W. Go, M.D.
Chairman, Nutrition Coordinating Committee
Office of the Director, NIH

INTRODUCTION

The National Institutes of Health (NIH) is the major agency in the Federal Government that supports research and training in nutrition as it relates to health maintenance, human development throughout the life cycle, disease prevention, and disease treatment. The NIH Program in Biomedical and Behavioral Nutrition Research and Training is supported by all 11 Institutes, the Division of Research Resources and the Fogarty International Center (FIC).

Nutrition is an important, crosscutting program area within the NIH. For this reason, the nutrition program is coordinated through the NIH Nutrition Coordinating Committee (NCC) that operates out of the Office of the Director and is advisory to the Director. Each year, the NCC prepares the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training for the preceding fiscal year and sponsors a major conference or workshop in nutrition that includes the interests of many Institutes.

The FY 1985 Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training is the ninth annual report prepared by the NCC. The report consists of five major parts and five appendices. In order to appropriately highlight the progress made in nutrition research in FY 1985, the major section in this year's report is section 2, "Highlights of the Nutrition Research Program and Program Development," which includes highlights of nutrition research according to stages of the life cycle as well as by specific diseases or conditions. One major difference between this report and those of previous years is the exclusion of the description of the extramural and intramural nutrition research program by Institute. Since the nutrition research priorities of the Institutes did not change significantly from those described in the FY 1984 Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, specific details of this research can be obtained in appendix C of the FY 1984 report.

Part I of the report, "Coordination of Nutrition Research at the NIH," presents the structure and mandate of the NCC, as well as the charges of its two subcommittees, the Program Subcommittee and Subcommittee on Nutrition Education. The Nutrition Policy of the NIH and the Definition of Nutrition Research, developed by the NCC in FY 1977, are also included in this section of the report. The role of the NCC office in coordinating the many aspects of nutrition research at the NIH is highlighted.

Part II of the report, "Highlights of the Nutrition Research Program and Program Development," begins with nutrition research highlights of particular scientific interest and importance. This year's highlights feature studies on maternal nutrition and fetal growth, infant nutrition and composition of human milk, the formulation of eating behaviors during adolescence and their role in the development of obesity, anorexia nervosa, and coronary heart disease, nutrition and

aging, and the assessment of nutritional status. In addition, important advances have been made in understanding the role of nutrition in the causes, prevention and treatment of various diseases and conditions, including obesity, coronary heart disease and hypertension, cancer, and oral diseases.

In terms of program development in nutrition, 35 new PAs, RFAs, and RFPs developed and published by the Institutes, as well as jointly through the NCC are listed. One particularly important announcement, the joint RFA "Core Grants for Clinical Nutrition Research Units" reissued by NIADDK, NCI and NIA in August 1984 led to the establishment in FY 1985 of three new CNRUs, one supported by NCI and two by NIADDK. Concluding part II is a description of the CNRU program, and a list of the 14 nutrition conferences sponsored by the Institutes and the NCC in FY 1985.

Part III, "FY 1985 Obligations for Nutrition Research and Training," briefly describes the data retrieval system, the Human Nutrition Research and Information Management System used for the third consecutive year by the NCC for the analysis of the nutrition program, both in terms of fiscal data and narrative research summaries. In FY 1985, another category was added to the existent 34 categories included in the HNRIM system, i.e., "Parenteral, Enteral and Elemental Nutrition" was added as category 35, and new codes (codes 51-56) were assigned to the special interest areas specific only to NIH. Included in this year's analysis is an overview of the entire nutrition research program; i.e., its distribution by the percentage of the nutrition component, by support mechanisms, by the 35 HNRIM classification categories and 6 special interest areas, and by extramural and intramural nutrition research and research training. Actual obligations for nutrition are compared with NIH obligations as a whole for three major components of extramural research, and for research training as well as fellowships.

Part IV presents highlights of the activities and accomplishments of the NCC, the Program Subcommittee, and the Subcommittee on Nutrition Education in FY 1985. The two workshops and one conference cosponsored by the NCC are highlighted, i.e., the workshop on "Old Problems and New Directions in the Evaluation and Management of Adverse Reactions to Foods and Food Additives," the workshop on "Genetics and Nutrition: Relevance to Learning Disabilities," and the conference on the "Health Effects of Polyunsaturated Fatty Acids in Seafoods." The conference was held June 24-26, 1985, and cosponsored by the National Marine Fisheries Service, National Oceanic and Atmospheric Administration, Department of Commerce; and the National Fisheries Institute. The Program Subcommittee's activities included participating in the planning meeting for this joint conference and the subsequent development of the third joint PA in nutrition with ADAMHA, entitled "Biological Mechanisms of Omega-3 Fatty Acids in Health and Disease States." The subcommittee members also provided input to a number of departmental nutrition activities including the revised edition of the USDA/DHHS pamphlet, "Nutrition and Your Health; Dietary Guidelines for Americans."

The Subcommittee on Nutrition Education reviewed three NIH nutrition publications intended for the public and, for the fifth consecutive year, was instrumental in the implementation of National Nutrition Month Activities at the NIH. The subcommittee also began planning for the "NIH Weight Loss Competition." The NIH-NCC Nutrition Research Exhibit, developed by the subcommittee and the NCC in FY 1983, was displayed and enthusiastically received at the annual meeting of the American Dietetic Association and numerous health fairs.

Each year the NCC and the NCC office staff provide input to congressional hearings on nutrition and respond to information requests about nutrition in general and about the NIH nutrition program in particular, from the Congress, other Federal agencies, the scientific community and the public. The NCC office staff represents NIH at various nutrition activities under way at the Office of the Assistant Secretary for Health; and presents the NIH nutrition program at national and international meetings, conferences, and workshops. Also described in this section of the report is the development of the Federal Human Nutrition Research and Information Management System, followed by highlights of the work accomplished through the Departmental Research Initiative in Nutrition and the Interagency Committee on Human Nutrition Research.

Part V consists of five appendices: appendix A presents the HNRIM classification system and the FY 1985 expenditures by HNRIM category and special interest area; appendix B presents the FY 1985 nutrition expenditures of the 11 Institutes, DRR, and FIC by support mechanism; appendix C describes the nutrition-related PA's, RFA's and RFP's; appendix D includes the summaries of the NCC scientific seminars; and appendix E includes the legislative authority of NIH for human nutrition research beyond FY 1985 in order to include the changes which resulted from Public Law 99-158 "Health Research Extension Act of 1985," which passed November 20, 1985.

The "Health Research Extension Act of 1985," amended the Public Health Service Act to revise and extend the authorities under that act relating to the NIH. The law reorganized the NIH by dividing the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases (NIADDK, as described in this report) into two new Institutes, i.e., the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Both of these Institutes will support those nutrition research areas consistent with their respective research missions. The law also established the National Center for Nursing Research.

A special debt of gratitude is extended to Dr. Artemis P. Simopoulos for her deligent work as chairman of the Nutrition Coordinating Committee from August 1978 until April 1986. Her dedication to the coordination and expansion of the NIH nutrition research program as well as the nutrition programs of all Federal agencies and Departments was instrumental to the advancement of nutrition science, and to the national and international recognition awarded especially to nutrition research at the NIH. Special acknowledgement is due to Dr. Tom Vogl for his pioneering development of the HNRIM system and his contributions to the NCC office until his departure in July 1986.

This report is completed and respectively submitted by the staff of the NCC September 26, 1986.

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I.

COORDINATION OF NUTRITION RESEARCH AT THE NIH

NUTRITION COORDINATING COMMITTEE AND SUBCOMMITTEES

The NCC, established in 1975, operates out of the Office of the Director and is advisory to the Director, NIH. The membership of the NCC consists of representatives from 11 Institutes, Fogarty International Center, Division of Research Resources, and Division of Research Services. Additional NIH offices and other agencies of the Department of Health and Human Services have liaison representatives to the committee. As of September 30, 1985, the NCC was composed of the chairman, 23 members and alternates, 8 liaison representatives and alternates from interested offices within the NIH, and 10 liaison representatives and alternates from other agencies within DHHS (see roster on pages vi-vii).

The mandate of the NCC is to review, stimulate and encourage the necessary support of nutrition research and training in order to better define the role of nutrition in the promotion of health, and the prevention and treatment of disease.

In FY 1977, the NCC developed the "Nutrition Policy of the NIH" and the "Definition of Nutrition Research at the NIH," which are still used by the NCC today. Each year, the NCC reviews and comments on the plans, execution, and results of pertinent Bureau, Institute, and Division research efforts relating to nutrition in order to develop the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training.

The NCC meetings are normally held once a month and are attended by the members, liaison representatives, and committee office staff. In addition to the regular business of the committee, special presentations on subjects of current interest to the NCC are frequently made by scientists from other agencies or professional groups such as the American Medical Association and American Institute of Nutrition, etc. The NCC meetings are followed by scientific seminars in nutrition in order to highlight or review research advances in nutrition. The seminar speakers include NIH grantees from the academic community as well as intramural scientists of the NIH and other Federal agencies.

The NCC office staff receives, analyzes and coordinates the many aspects of nutrition research and training at the NIH. The office staff provides information on the NIH nutrition research program and on various topics of nutrition research to a broad spectrum of sources such as the Congress, the Executive Branch, including various agencies of the Public Health Service, the scientific community and the public.

The mandate of the NCC, the charges of the Program Subcommittee and the Subcommittee on Nutrition Education, the nutrition policy of the NIH, and the definition of nutrition research follow.

MANDATE OF THE NUTRITION COORDINATING COMMITTEE

The Nutrition Coordinating Committee:

- Reviews and comments on the plans, execution, and results of pertinent Bureau, Institute, and Division research efforts relating to nutrition in order to develop the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training.

- Processes and responds to incoming requests for nutrition information from the DHHS and other Federal agencies, the Executive Branch of the Government, the Congress, outside institutions, and the public.

- Maintains up-to-date information on funding and on intramural and extramural research and training activities in nutrition.

- Develops and monitors means for improving the coordination of these activities.

Within the scope of the major activities described above, the NCC has the following specific functions:

- To define nutrition research at the NIH. (Accomplished, see page 7.)

- To develop a policy statement for research and training in nutrition at the NIH. (Accomplished, see page 5.)

- To establish information exchange. Each representative presents to the NCC any new plans, activities, conferences, and workshops that are concerned with nutrition. Future workshops and conferences are discussed to ensure full participation of all relevant Institutes; when many Institutes are involved, the NCC sponsors or cosponsors such workshops or conferences. Through the information exchange mechanism, the NCC identifies areas of collaboration for further research. The NCC informs the NIH nutrition community of all meetings, both within and outside NIH, concerned with nutrition. The committee, if requested, also reviews and comments on nutrition reports generated by the NIH and by other Federal and non-Federal agencies.

- To develop a data retrieval system for research and training in nutrition. (Accomplished, see page 59.)

- To review proposed legislation and regulations. The NCC develops mechanisms for receiving, reviewing, and distributing information on proposed legislation affecting nutrition policy.

- To develop and maintain effective liaison with other departments and agencies that have nutrition activities. The NCC assesses existing liaison mechanisms and identifies those departments and agencies requiring a liaison relationship. Liaison representatives provide information to the NCC.

- To encourage the application of nutrition research to practice. The NCC members identify research data that are ready for "technology transfer" and promote the appropriate application of new knowledge in nutrition.

- To promote the dissemination of information for the purpose of public education on the role of nutrition on health and disease. The NCC assists in coordinating Bureau, Institute, and Division efforts in nutrition education and acts as a focal point for the dissemination of nutrition information to the public.

CHARGE OF THE PROGRAM SUBCOMMITTEE

- To develop joint program announcements

- To consider nutrition conferences

- To discuss the advisability of outside speakers for the scientific seminars at the NCC meetings.

CHARGE OF THE SUBCOMMITTEE ON NUTRITION EDUCATION

- To review NIH nutrition publications designed for the public

- To develop public service announcements

- Develop and implement National Nutrition Month activities at NIH.

NUTRITION POLICY OF THE NIH

Policy Objectives

The NIH supports DHHS policy by sponsoring and conducting biomedical research designed to improve the quality of life for all Americans through optimal nutrition. Basic biomedical nutrition research will develop knowledge needed to promote and maintain health, as well as to prevent and treat disease.

Nutrition research has passed through two stages and is now entering a third. The first stage saw the discovery of vitamins and the development of many of the basic nutritional requirements. The second stage reduced nutrition to subcellular and molecular terms within areas of biochemistry and physiology. The third stage calls for a synthesis of newer findings for translation into practical information to assist the individual to develop normally, to avoid disease, and to live as long and as healthy a life as possible. For this third stage, knowledge is needed that will permit distinction among individuals in terms of genetic differences that affect dietary requirements.

Areas of Emphasis

Current nutrition research at NIH concentrates on eight critical areas:

1. Clinical Nutrition Throughout the Life Cycle. Research in this initial area examines variations in nutritional requirements to promote and maintain health during all phases of the life cycle. Within the clinical nutrition program, research is also directed towards elucidating the effects of infant feeding practices and infant nutrition on subsequent physiological, immunological, and mental development. Another research goal involving the life cycle is to understand the effects of maternal nutritional status and maternal diet before and during pregnancy on the development of the fetus. In order to understand the ramifications of this nutritional problem, more must be learned about the interaction between the genetic makeup of an individual and his dietary intake. Special emphasis is given to studies on the role of nutrition in health of the aged and aging process, particularly the effects of aging on nutrient utilization, digestion, absorption, and metabolism, and nutrition and age-related mental deterioration.

2. Role of Nutrition in Disease Development. The NIH conducts research on mechanisms by which dietary deficiencies, imbalances, and excesses lead to the development of physical and mental diseases and disorders.

3. Prevention of Disease. The NIH has assumed a leading role in shifting the emphasis in nutrition research from curing disease after symptoms have developed to preventing or delaying the onset of disease. Continued research emphasis is given to malnutrition in all its guises, including under- and overnutrition, obesity, food faddism, and specific dietary deficiencies.

4. Treatment of Disease. The NIH develops nutritional therapies for specific diseases such as cancer, gastrointestinal disorders, obesity, osteoporosis, renal insufficiency, atherosclerosis, and inborn errors of metabolism. Improved methods are being developed to provide general nutritional support for newborns of low birth weight who may require parenteral supplementation and for elderly, disease-ridden, traumatized, or postoperative patients who may require total parenteral nutrition or elemental diets.

5. Technology Transfer. An important component of the NIH nutrition policy is to assure appropriate application of research in practice. To expedite transfer of nutrition technology, the NIH is establishing mechanisms to evaluate research data relevant to nutrition and public health.

6. Nutrition Education. The NIH continues to support research in nutrition education as byproducts of clinical trials and demonstration projects; by the education of the physician through professional societies, scientific meetings, and journals; and by the production of nutrition education materials for the health educator

and the public. Encouragement of positive nutrition behavior is an obvious task for educators of children, young adults, and the elderly.

7. Research Training. The NIH encourages and supports the teaching of modern biochemical nutrition at the pre- and postdoctoral levels. This training includes the disciplines upon which nutrition research is based such as gastroenterology, endocrinology, metabolism, developmental biochemistry, genetics, and molecular biology. The NIH also promotes expanded training programs in basic and clinical nutrition research aimed principally at the physician investigator and clinically oriented biomedical scientists.

8. Coordination. The NIH cooperates in establishing mechanisms for interagency coordination. Nutrition research at the NIH is coordinated through the Nutrition Coordinating Committee. Institutes initiate their own nutrition programs within their appropriated budgets. The committee seeks agreement on critical issues of definition, comments upon individual programs identified to it, maintains an information exchange (mechanisms for program development), promotes liaison with other Federal agencies, and encourages coordinated program planning among Institutes and with other appropriate agencies. The committee assists in the development of nutrition data retrieval systems, and reviews legislative and regulatory initiatives that impact upon human nutrition research.

DEFINITION OF NUTRITION RESEARCH AT THE NIH

Included in the first report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1977, issued by the NCC, was the definition of biomedical and behavioral nutrition research that the NCC developed. That definition, which continues to serve as a basis for data retrieval and for the assessment of information about the nutrition research and training activities of the NIH, is as follows:

> "The term nutrition research includes studies designed to assess the consequences of food or nutrient intake and utilization in the intact organism, including man, and the metabolic and behavioral mechanisms involved. These studies encompass investigation of nutrient variables at the cellular or subcellular level. This definition also includes:
>
> - Research designed to elucidate the metabolic role or function of nutrients in both animal models and man.
>
> - All studies concerned with genetic-nutrient-environmental interactions where a nutrient is a variable.
>
> - Dietary studies expected to produce significant changes in health status, including the maintenance of health and the treatment of disease in man. Such studies might include clinical trials, epidemiological studies, metabolic studies, surveillance, and nutritional status monitoring studies."

II.

HIGHLIGHTS OF THE NUTRITION RESEARCH PROGRAM AND PROGRAM DEVELOPMENT

NUTRITION RESEARCH HIGHLIGHTS

Over the past year, significant advances have been made in understanding the role of nutrition in health promotion and in the etiology, prevention and treatment of various diseases and conditions throughout the life cycle. Studies on the relationships between maternal nutrition and fetal growth have revealed the significant impact of the nutritional status of the mother on the growth and development of the fetus. In the area of infant and child nutrition, studies have considered the appropriateness of infant feeding practices and formulations, i.e., breast feeding versus formula feeding of the premature infant; the role of nutrition in respiratory distress syndrome and retrolental fibroplasia; nutritional therapy for the inborn errors of metabolism; and the possible effects of nutrition on childhood hyperactivity.

Since eating habits formed during adolescence often remain into adult life, and therefore impact on disease risk, investigators also have focused on the formulation of eating behaviors during adolescence and their role in the development of obesity, anorexia nervosa, coronary heart disease, etc. In order to obtain a better understanding of nutrition's role in aging, investigations have been carried out on the nutrient needs of the elderly as they relate to longevity, immune function, osteoporosis, senile cataracts, age-related maculopathy, and gyrate atrophy.

Progress also has been made on the development of better methods for the assessment of nutritional status throughout the life cycle; in understanding the different functions and interrelationships of the vitamins, minerals and trace elements; in elucidating the interaction of nutrition and behavior, and the role of nutrition in the development and function of the central nervous system.

In addition, important advances have been made in understanding the role of nutrition in the causes, prevention and treatment of various diseases and conditions, including obesity, coronary heart disease and hypertension, cancer, and oral/dental diseases.

MATERNAL/FETAL NUTRITION

It is now an accepted tenet that the nutritional status of the mother affects not only the growth and development of the child, but her own health as well. For example, maternal vitamin A status has been shown to affect placental transport of vitamin A to the fetus, while protein intake affects levels of retinol-binding protein and, thereby, circulating vitamin A levels. Maternal vitamin A levels in the blood appear to fluctuate during pregnancy and vary with dietary intake. Most vitamin A circulates in the blood as retinol, bound to plasma retinol-binding protein (pRBP) which is synthesized in liver, where it is complexed with retinol. Excessive maternal vitamin A intake and high maternal vitamin A stores have been shown to suppress placental transport of vitamin A, whereas low stores increase its transport. Thus, since vitamin A transport, storage, and utiliza-

tion depend to a large extent on protein, future studies of vitamin A metabolism in the maternal-fetal-neonatal unit should include examination of the effects of maternal protein intake.

Studies have also been conducted on the effects of the mother's nutritional status on pregnancy outcome. Particularly relevant in this research are the effects of vitamin and mineral deficiencies during pregnancy and lactation. Folate deficiency is being examined in female monkeys during gestation and lactation for its effects on plasma and red blood cell folate levels, the development of megaloblastic anemia, and levels of formiminoglutamic acid excretion in both the mother and infant. Investigations are also under way on the effects of zinc, copper, and manganese deficiency in mammalian fetal development. Recently, maternal dietary deficiency of manganese has been shown to result in fetal death and malformations. In some of these cases the zinc content of the fetuses was lower than normal, thereby providing some evidence that the malformations seen in manganese deficiency might be related to deficiencies in the supply of zinc. However, when zinc was added to manganese-deficient diets, neither the fetal absorption rate nor the proportion of malformed fetuses in the low-manganese group was affected. Thus, the teratogenic effect of low dietary manganese does not appear to be due to secondary zinc deficiency.

Recent studies in animals have provided evidence that dietary omega-3 polyunsaturated fatty acids (PUFAs) are essential for normal prenatal and postnatal development of the retina and brain. Animals cannot create double bonds at the omega-3 and omega-6 positions, and are therefore dependent upon dietary sources for these fatty acids. Omega-3 fatty acids comprise a group of highly polyunsaturated and very long chain fatty acids that are prevalent in all marine fish and seafood. They are found in particularly high concentrations in salmon and mackerel, and are also found in green leafy vegetables such as spinach, kale and romaine lettuce, and in a few vegetable oils like soybean. Eicosapentaenoic acid, or EPA (20:5 omega-3), and docosahexaenoic acid, or DHA (22:6 omega-3), are the two most common omega-3 fatty acids studied to date.

In one study, female rhesus monkeys were maintained on semipurified experimental diets for a minimum of two months before conception and then throughout pregnancy. To induce omega-3 PUFA deficiency, a diet supplying less than 0.3 percent of total fatty acids as linolenic acid was used. The control diet contained 8 percent of total fatty acids as linolenic acid. No significant differences were seen between groups in the mother's weight gain during pregnancy, the infant's birth weight, or the infant's body length or skull circumference at birth. The infant monkeys were then fed the omega-3 PUFA deficient diet for almost 2 years and their visual function was tested behaviorally by measuring visual acuity at 4, 8 and 12 weeks of age. The depletion of omega-3 fatty acids was correlated with a significant functional deficit. Deficient animals adapted to the dark showed markedly greater diminution of response amplitudes on electroretinograms (ERG) when brief bright flashes were repeated at short intervals. In other words, the deficient animals showed a

doubling of the time required for the ERG to recover to its maximal amplitude after a flash.

The reduced content of DHA in the retina may produce alterations in the physical and functional photoreceptor properties in neuromembranes, which may underlie the visual deficits found in these deficient animals. One possible explanation for this phenomenon is that the omega-3 fatty acids render cell membranes more fluid, possibly enabling the cells to react more quickly to electrical or chemical signals. These fatty acids are particularly concentrated in the membranes of photoreceptor cells in the retina and nerve synapses, where nerve impulses are conveyed from one neuron to the next. In the monkeys fed the deficient diet, other types of fatty acids replaced the omega-3 compounds in the cell membranes which might hamper some of the reactions that occur within or on the membrane surface.

Some animals on the omega-3 deficient diet also showed very low levels of omega-3 fatty acids in brain cells and blood, while the amount of omega-3 fatty acids in the liver, skin and fat cells was approximately 5 to 20 percent of the levels found in control animals. Further research is needed in order to determine the relative contributions of prenatal and postnatal deprivation to the observed visual deficit, and to determine the degree to which the biochemical and functional effects of omega-3 fatty acid deficiency are reversible. Current studies are being conducted to determine the reversibility of these findings and to determine which fatty acids in the omega-3 series can best be used to correct these abnormalities.

Also being tested in the rhesus monkey is the possibility that the omega-3 PUFAs similarly affect the stimulation of brain cells involved in learning and behavior. Because omega-3 fatty acids are prevalent in the cerebral cortex of the brain, a nutritional deficiency of the omega-3 compounds might impair intellectual functions, such as the ability to learn and reason, as well as overall intelligence. Preliminary observations of the monkeys deficient in omega-3 fatty acids indicate no impairment of the animal's learning ability, however, further testing will be pursued with more finely tuned tests of the monkey's intellectual functions and behaviors. Other investigators have shown that rats fed a diet deficient in omega-3 PUFAs did not learn to run a maze as well as rats fed a control diet.

The proven benefits of omega-3 PUFAs in primates and the dangers of deficiencies underscore the importance of these fatty acids in the human diet. The minimum amount of the omega-3 PUFAs required in the diet throughout the life cycle, including during pregnancy, lactation and infancy has not been determined and the optimal balance of omega-3 and omega-6 fatty acids also needs consideration.

INFANT AND CHILD NUTRITION

Every child is a product of his or her genetic background which must bear the environmental influences of the time; nutrition is one environmental factor that plays a major role in the proper growth and development of infants and children from the day they are born.

Thus, the determination of the nutrient requirements for infants and children and the development of appropriate nutritional therapies, particularly for the premature, and very low birth weight infants, is an important research area. Today, emphasis is placed on understanding the biochemical and metabolic events that undergird nutrition, while at the same time studies are also examining the interaction between nutrients and the development of the whole organism.

Research on the nutritional and other health benefits of human milk for the young infant has led to important findings. The complicated composition of human milk and colostrum, as well as their relationship to the metabolic needs of the newborn, has been established. Studies have shown that prolactin, a polypeptide hormone secreted by the lactotrope cells of the anterior pituitary gland, acts on breast tissue to cause its development, differentiation, and milk production. Investigators have also isolated and purified the prolactin receptor protein, and are using the DNA recombinant technique of oligonucleotide mutagenesis to identify the bioactive sites of the hormone and its receptor. Studies of the neuroendocrine control of prolactin synthesis and its release by hypothalamic hormones, such as thyrotropin-releasing hormone (TRH) and prolactin inhibitory factor (PIF), have shown hypothalamic tripeptide TRH to be more potent in stimulating the lactotropes than the thyrotropes of the pituitary gland. In addition, the adrenergic neurotransmitter, dopamine, has been shown to act as one of the prolactin inhibitory factors.

The mechanisms of breast feeding are also being investigated in terms of the mother's central integration of signals from the peripheral nervous system that are triggered by the infant's smell, sound, touch, and nipple stimulation, as well as by the intraductal pressure that builds up in the breast between feedings. The mechanisms by which the brain transduces this sensory input into the synthesis and release of oxytocin by the neurohypophysis is of particular interest. Oxytocin appears to be carried in the bloodstream by its binding protein, neurophysin, to the breast where it initiates milk let-down at the commencement of feeding.

Studies aimed at understanding the biochemical immaturity of premature infants are particularly relevant to the development of appropriate enteral and parenteral feedings. Several studies are exploring the nutrient requirements of the premature infant and whether they differ from those of full-term infants. One component of this research involves investigations on the appropriateness of human milk versus infant formula for the premature infant with a developmentally immature gastrointestinal tract. Human milk contains enzymes, particularly lipases, which have been shown to work in conjunction with the normal infant's oral and intestinal lipases to digest the lipids contained in milk, as well as to attack lipid surfaces on various intestinal parasites. Since it is not known whether the developmentally immature gastrointestinal tract of the premature infant can carry out similar interactions, studies are examining whether human milk may be suitable for feeding the premature infant, and whether it provides unique health values when compared to synthetic formulas.

Another item of interest is the composition and possible health benefits of breast milk of mothers who deliver premature infants.

Research in developmental gastroenterology focuses primarily on the processes of digestion, absorption and transport of nutrients by infants and children. These processes develop over time in order to accomodate changing growth needs from birth through adolescence. Studies to elucidate the function of cellular systems responsible for the transport of large molecules through the lining of the small intestine indicate that such processes are associated with specialized intestinal cells and are selective to the types of molecules transported. These findings have been important to the understanding of the causes of various malabsorption syndromes and food intolerances that are responsible for a large amount of infant morbidity.

Other studies on malabsorption, particularly of trace elements associated with infant formula feeding, are under way in infant rhesus monkeys, a model particularly suitable for studying the absorption of iron and zinc by human infants. Evidence exists that the milk of rhesus monkeys is virtually identical to that of human mothers and that the mechanisms of absorbing trace elements in both species are also probably identical. Studies are currently under way using radioactive tracers in the rhesus monkey model to identify the factors in infant formulas derived from cows milk and soybean that interfere with the absorption of iron, zinc and other trace elements, as well as the relationship of these factors to trace element transport mechanisms.

The importance of adequate levels of taurine in infant formulas has also been established using infant rhesus monkeys. Taurine is notably absent or low in certain vegetable-based formulas, as well as in cows milk following the immediate postpartum period of lactation. Deficiencies in taurine have been linked to the degeneration of retinal photoreceptors in the cat. Similar changes also have been found in infant rhesus monkeys given infant formula low or deficient in taurine. These research results have already led some manufacturers to supplement infant formula with taurine.

The best form of infant feeding, i.e., cows milk, breast-feeding, or soy-based infant formulas, during the treatment of acute diarrhea illness in infants remains controversial. Some children have been shown to experience severe diarrhea following the early introduction of undiluted lactose-containing cows milk or formula, and thus may better tolerate the gradual introduction of dilute lactose-based formula. Studies conducted in Asia have demonstrated that infants breast-fed during their diarrheal illness had a reduced number and volume of diarrheal stools when compared to infants whose feeding was withheld for twenty-four hours. It is still not known why infants tolerate the lactose in human milk better than the lactose in cow milk. In other studies comparing the response of children fed soy-based, lactose-free formulas to infants receiving standard therapy (food withheld during the first 48 hours), children fed the soy-based formulas experienced a shorter duration of illness and over a 50 percent decrease in stool output.

Despite major advances in diagnosis and treatment, respiratory distress syndrome (RDS) is the third leading cause of infant death in the United States. The underlying cause of RDS is an inadequate supply of the natural substance, surfactant, which normally coats the inner lining of the lung. Inadequate amounts of surfactant cause the collapse of the lung's air sacs, forcing the infant to fight for every breath.

Research under way on neonatal lung disease at one of the Specialized Centers of Research (SCOR) is attempting to devise methods to ensure normal lung development. Understanding how nutrition affects respiratory functions is included in this research. A deficiency, as well as an overabundance of certain food components, has been shown to influence surfactant synthesis, and thereby impact upon the newborn's risk of RDS and the chance for recovery. Throughout pregnancy, the fetus stores certain nutrients, particularly fats and vitamins, that are needed after birth. Premature babies, therefore, may not accrue sufficient stores of nutrients, particularly vitamins A and E, and fatty acids, before birth. Vitamins A and E, present in lung tissue, may play important roles in cellular functions crucial to respiration, while fatty acids provide about 85 to 90 percent of the carbon atoms in the surfactant molecule.

Studies have shown that improvements in the premature newborn's nutritional status, particularly in terms of these nutrients, might be particularly important in preventing RDS. Dietary improvements provided soon after birth may help reduce the severity of RDS, and possibly prevent chronic lung disease that often results later in life. Intravenous methods have been devised that increase vitamin E levels of premature babies with RDS to normal within 2 days; similar methods are being studied for increasing vitamin A levels and for the administration of fatty acids.

Investigations are also under way to provide insight on how diabetes in the expectant mother affects the timing of fetal lung maturation and the synthesis of surfactant. Women whose diabetes is poorly controlled during pregnancy are six times more likely than nondiabetics to deliver babies with RDS. Animal studies have shown that increased levels of insulin can delay fetal lung maturation and that elevated blood glucose, which is characteristic of these infants, might also be a factor in the development of RDS.

The possible role of vitamin E in reducing the incidence and severity of retrolental fibroplasia, otherwise known as retinopathy of prematurity, is also being evaluated. The role of vitamin E in animals with canine vitamin E deficiency retinopathy has been investigated to characterize the development and progression of this disease in animals, and as an aid in understanding vitamin E's role in human retinal tissue.

Evidence now suggests that atherosclerosis begins in early life. One hypothesis being investigated is whether the high cholesterol content of breast milk sets up homeostatic mechanisms that allow for effec-

tive cholesterol metabolism in adult life. Commercial formula, which is low in cholesterol, is the predominant infant feeding mode in the United States. An epidemiologic study is under way to examine the relationship between type of infant feeding method and serum cholesterol levels of children ages 4 to 11 years. The advantages of this study are that it includes a large heterogeneous sample; important confounding factors such as current diet and weight; a broad childhood age span; and generalizability of results to the U.S. population. It is hoped that the findings from this study will help to identify early dietary determinants of childhood serum cholesterol levels.

The development of appropriate dietary therapies for newborn infants suffering from one of the many inborn errors of metabolism is particularly important. Studies concerned with the enzymatic defects of the urea cycle have examined the combination therapy of diet and drugs. In deficiencies of the urea cycle enzymes, the liver's inability to process ammonia into urea results in vomiting, lethargy, respiratory distress, and seizures. These infants eventually lapse into a coma. One new therapy, combining diet with drugs, phenylacetate, benzoate, or citrulline, has been found to stimulate alternative metabolic pathways that bypass urea cycle defects and lead to the excretion of nitrogen-containing compounds, that would otherwise accumulate as ammonia. These alternative metabolic pathways are less efficient, however, than the urea cycle in excreting nitrogen, and thus nitrogen intake of the infants must be limited. However, infants given large doses of sodium phenylacetate, the drug most effective in eliminating nitrogen wastes, have been shown to excrete more nitrogen, thereby reducing the danger of occasional hyperammonemia. These infants can also consume more nitrogen, and thus improve the quality of their diets. In addition, since arginine is an essential amino acid and is not produced by infants with urea cycle deficits, dietary supplements of arginine or citrulline, which the body converts to arginine, must also be provided. Research results to date have shown this therapy to be effective in extending the lives of infants afflicted with urea cycle disorders.

A related disorder, lysinuric protein intolerance, interferes with the operation of the urea cycle through a defect in the absorption of dibasic amino acids, producing osteopenia or demineralization of bone. Dietary supplementation with citrulline has been found to increase protein tolerance, accelerate linear growth, increase bone mass and improve general well-being of infants suffering from this disorder.

Several coordinated field studies are under way to determine the effect of malnutrition during pregnancy and infancy on the growth and mental development of children, the effects of nutritional interventions in these children, and the relative importance of calorie versus protein deficits for the normal birth weight and growth of young children. Early findings indicate that nutritional supplementation, home stimulation, or a combination of both early in life contributes to earlier school entry and a greater likelihood of passing from first to second grade. Maternal training was also found

to contribute to a better nutritional intake by the child at 7 years of age, 3 years after supplementation was terminated.

The possible relationship between sugar consumption and childhood hyperactivity is a controversial but important topic, since per capita sugar consumption has been increasing steadily for the past 25 years. According to recent studies, sugar consumption does not appear to cause or even aggravate the aggressive behavior of hyperactive children. One study included two groups of hyperactive boys, ages 7 to 12 years. On the first day of the challenge, one group was given beverages containing sucrose, while the other group was given drinks of comparable sweetness, but containing the sugar substitute aspartame. On the second day, the situations were reversed. No significant differences were found between measures of learning, attention and impulsiveness, which have been demonstrated as sensitive indicators of hyperactivity, of the two groups of subjects or between scores achieved in baseline testing and those recorded after the sucrose or aspartame challenges. Thus, neither the sugar nor the artificial sweetener appeared to significantly affect the boys' behavior.

Results from the continuous performance test, used to measure whether sugar ingestion resulted in a relatively rapid allergic response or a slower hypoglycemic reaction (the proposed physiological mechanisms by which sugar would cause hyperactivity), indicated that the scores of the boys challenged with sucrose were not significantly different from those of the boys given the artificially sweetened beverages.

Another study included hyperactive boys of grade school age who were fasted overnight and then given a challenge drink in the morning without any other food. The data did not reveal any significant differences for any of the 37 behavioral variables tested. Thus, sugar ingestion did not apppear to negatively affect behavior. In fact, another study of a larger number of boys who ingested sucrose indicated that they made significantly fewer errors on a line drawing test designed to measure impulsive behavior compared to boys consuming aspartame. Similarly, in a study of the performances of hyperactive boys whose parents consciously restricted their sugar intake, sugar challenges resulted in significantly fewer attention shifts during play periods.

Although the findings from these studies provide evidence that sugar consumption does not cause these hyperactive boys to behave inappropriately, a small subgroup of hyperactive children may be particularly sensitive to sugar. Long-term controlled studies of all dietary variables are needed to further explore the potential consequences of sugar ingestion on the behavior of hyperactive children. One study includes 400 normal 4-year-old boys and girls, both black and white, who will provide dietary histories that emphasize sugar-containing foods for seven-day periods. Behavioral function and activity are being assessed in the children as well as parental characteristics, attitudes, and behaviors. The data from this study should contribute significantly to our understanding of the role of sugar consumption in hyperactivity.

Vitamin A deficiency is the leading cause of childhood blindness in developing nations throughout the world. In order to further elucidate the specific mechanisms involved in this blindness, projects are under way to determine the normal fluxes/movements and metabolism of vitamin A, as well as other nutrients, in the retina and retinal pigment epithelium. The efficacy of various retinoids, or vitamin A analogues, in treating experimental xerophthalmia, a drying of the cornea and conjunctiva associated with vitamin A deficiency, is also being investigated in animals. In addition, the role of infection and inflammation is being examined in the development of keratomalacia, a sight-threatening drying and softening of the cornea resulting from prolonged vitamin A deficiency. Other studies being conducted with the National Institute of Nutrition in Hyderabad, India, are attempting to define other factors, in addition to vitamin A deficiency, that increase a child's risk of nutritional blindness and to evaluate the efficacy of various forms of dietary supplementation.

In clinical studies of children with cystic fibrosis (CF), attempts are being made to define more precisely the abnormalities that contribute to the pulmonary and gastrointestinal symptoms of this disease. Lingual lipase activity is being studied in order to further clarify its role in fat absorption in these patients, while serum amylase and its isoenzymes, and immunoreactive trypsinogen and lipase are also being analyzed for diagnostic purposes. Elevated basal hydrogen (H_2) in expired air may reflect passage to the colon of excessive amounts of dietary sugars and glycoproteins metabolizable to H_2.

In investigations to examine the effect of complex carbohydrates consumed the previous evening on basal H_2 excretion by CF patients, wheat and beans were shown to increase basal H_2 excretion in CF patients but not in control individuals. After a rice meal basal H_2 remained elevated (> 42 ppm) in CF patients with bacterial overgrowth while in healthy persons rice starch caused uniformly low breath H_2 values (<3 ppm) in healthy subjects. These results indicate that previously ingested dietary substrates containing complex carbohydrates influence basal H_2 concentration. Elevated basal H_2 values in CF patients may reflect excessive amounts of carbohydrate-containing proteins in the colon, or the presence of small bowel bacterial overgrowth. These results also indicate that conditions for measurement of basal H_2 might be standardized using the previous dinner meal.

In another study, rice pancakes containing 100 grams carbohydrate per test meal were given to 5 CF patients ranging in age from 13 to 26 years and expired air was monitored for 8 hours following ingestion. A rise in H_2 > 10 ppm above baseline was observed in each subject from 5 to 8 hours after rice starch administration. These data are consistent with the malabsorption of starch observed in CF subjects, since ingestion of rice starch does not result in H_2 production in normal subjects. In addition, an early rise (< 2 hours) in H_2 production was also demonstrated in two subjects, which suggested the

presence of small bowel bacterial overgrowth in some subjects with CF.

ADOLESCENT NUTRITION

Adolescence is the stage of profound physiological and psychological changes some of which impact upon the dietary habits of the adolescent. These habits are influenced in part by environmental factors such as peer pressure and fear of rejection. A better understanding of the processes that determine patterns of food consumption during adolescence is important to the promotion of more healthy food choices by adolescents and, perhaps, better adult health.

A study involving 400 adolescents, 11 to 12 and 15 to 16 years of age, will include measurements such as repeat 24-hour food consumption patterns, anthropometrics, self-perception of body weight/fatness, individual decisionmaking processes regarding food choices, ratings of foods in terms of the criteria of choice, and cognitive development and personality characteristics. The results will facilitate the establishment of health promotion and nutrition education programs for this age group. In addition, the project represents a new conceptual approach to the study of food choices and habits, and to the development of new methodologies.

The common eating disorders of obesity, anorexia nervosa and bulimia, are of particular concern in the adolescent. One study of obese adolescents designed to develop optimal dietary therapy compares the effects of a diet containing protein plus glucose with an isonitrogenous diet made isocaloric with fat. The effects of these two diets on the dynamics of glucose and protein metabolism are being examined before and after each dietary period by direct measurements of the synthesis and catabolism rates of whole-body protein. The method used is a primed constant infusion of ^{15}N-lysine with a simultaneous prime of the urea pool with di-^{15}N-urea. The results of this research will permit an assessment of optimal dietary protein, and contribute to the understanding of the metabolic responses to hypocaloric dietary therapy in obese adolescents.

Studies on the role of diet during adolescence in the development of coronary heart disease are also under way. A study on the antecedents of atherosclerosis during adolescence is examining the relationships between diet and changes in adiposity, sex hormones, lipids, lipoproteins (HDL_C), and apolipoproteins in 500 males 10 to 14 years of age. Recent studies have shown that HDL_C levels significantly decrease during sexual maturation. These longitudinal studies will permit an assessment of adolescent changes in lipid profiles and of the relationships of these changes to sex hormones and adiposity in normal and high-risk adolescent males.

NUTRITION AND AGING

Heredity establishes the foundation for the body's ability to cope with the psychophysiological changes that occur with aging, however

nutrition may make the foundation stronger and more resistant to such changes. A major research question is whether nutritional needs change significantly with age and, if so, how do these needs change and what specific nutrients are involved. In the area of nutrition and aging, basic and clinical investigations are under way on the effects of nutritional factors throughout the life span on longevity and age-associated morbidity; the assessment of nutritional status in the elderly; the effects of aging on nutrient digestion, absorption, and utilization; and the contribution of nutritional status to the etiology and pathogenesis of diseases prevalent in the elderly.

Studies on the effects of nutrition on longevity have been under way in animals for many years. Dietary restrictions have been shown to extend the life span in laboratory rodents, but, the mechanisms of this effect are not yet understood. Early studies suggested that restriction of protein intake might be the critical factor. However, recent data have implied that protein restriction, in the absence of overall caloric restriction, delays the onset of disorders such as cardiomyopathy and nephropathy but not of neoplasms. Calorie restriction, however, delays the onset of all three pathobiologies. Thus, more than one biological mechanism may be mediating the effects of dietary restriction on longevity.

Other studies have considered whether the timing of the dietary restriction affects longevity. Studies in rats have shown that dietary restriction begun pre- or postsexual maturity was as effective in prolonging the life span. These, and similar findings in mice, confirm that the effect of dietary restriction on extending the life span does not depend on the delayed maturation seen in animals whose diet is restricted immediately after weaning.

Recent data from animal studies have shown that once a stable body weight is achieved, both restricted and ad libitum-fed animals consume the same number of calories per gram of lean body mass. This finding suggests that dietary restriction may extend the life span through complex interactions at the tissue, organ, or organism level rather than a general slowing of cellular intermediary metabolism.

Future studies may be able to clarify nutrition's role in immune function that may relate to the increased incidence of certain diseases and conditions prevalent in the aged population. Improvements in immune function in older persons have been shown following increased zinc intake. However, recent findings indicate that zinc supplementation may have detrimental effects in some older people. For example, zinc supplementation appears to diminish circulating levels of HDL cholesterol in elderly people who exercise. Zinc may affect the intestinal absorption of calcium. In one study, 140 mg/day of supplemental zinc decreased intestinal absorption of calcium during a period of low calcium intake (200 mg/day), but not during a period of normal calcium intake (800 mg/day). Further investigation is planned to determine the specific dose of zinc and calcium intake at which supplemental zinc inhibits the intestinal absorption of calcium, and the mechanisms of action. The clarification of zinc's effect on calcium absorption becomes important in

view of the widespread use of zinc supplements of unknown dosage by the public. This problem is particularly pertinent to the elderly whose intake of calcium may be lower than that recommended.

Many older people have been found to have marked deficiencies in vitamin D and calcium, two nutrients implicated in the pathogenesis of osteoporosis and osteomalacia which are often found in older persons. Recent data indicate that 61 percent of the women and 50 percent of the men consume less than half of the Recommended Dietary Allowance (RDA) for vitamin D. The mean plasma levels of 25-hydroxyvitamin D in these older individuals were approximately half those in younger subjects. Since adequate levels of vitamin D are important for the maintenance of adequate bone density, deficiencies in the vitamin appear to increase the risk of hip fracture. And, although some vitamin D is made in the skin in response to sun exposure, the capacity of the skin to make vitamin D appears to diminish with age. In terms of calcium intake, 75 percent of the women and 55 percent of men consume less than the RDA for calcium.

Studies of osteoporosis in postmenopausal women have shown that daily doses of as little as 0.5 microgram of 1,25-dihydroxycholecalciferol to postmenopausal women with osteoporosis increased calcium balance and trabecular bone volume, and decreased bone fracture rates. In women after age 50, especially in those who were postmenopausal, plasma levels of the 1,25-dihydroxycholecalciferol decreased significantly. Estradiol treatment of these women causes a 30 to 40 percent increase in circulating levels of 1,25-dihydroxycholecalciferol and a corresponding increase in calcium absorption. Other studies have shown alpha-hydroxycholecalciferol effective for the treatment of postmenopausal osteoporosis, since the alpha form is readily converted by the liver into the active 1,25-dihydroxy form.

The role of nutrition in the development of age-related cataracts, i.e., the opacification of the lens which occurs with aging is being investigated in a number of animal studies. The results of this research have shown that deficiencies in vitamin E and tryptophan cause the formation of cataracts different from those associated with diets deficient in tryptophan alone. It is thought that cataracts may also result from light-induced oxidation, which causes toxic products to accumulate and damage the lens tissues. Selenium-deficient diets may provide another stress that may lead to an increased incidence of cataracts. To further delineate the mechanisms by which oxidation may cause cataracts, investigations are under way on protein synthesis and metabolism in the lens, and on the effects of selenium and vitamins C and E which act as antioxidants in protecting the lens against oxidative stress.

Age-related maculopathy (ARM) is a degenerative disease of the macula, a highly specialized portion of the retina which enables sharp central vision, and is the leading cause of new cases of blindness in people aged 65 years and over. One of the major age-related changes in the retinal pigment epithelium is the progressive accumulation of lipofuscin, or age pigment, which is thought to contribute to macular degeneration. Studies in rats are under way to study the nutrient

factors responsible for the lipofuscin accumulation. The other major change observed in ARM is progressive photoreceptor degeneration; deficiencies in vitamins A and E, taurine, selenium, and zinc appear to lead to the buildup within the photoreceptors of oxidative products, which subsequently damage the photoreceptor membranes. The efficacy of administering vitamins E and C to patients who already have severe visual loss in one eye due to ARM in protecting their good eye from visual loss is being studied. Other investigators are studying whether selenium supplementation can also arrest the progression of the disease.

Gyrate atrophy of the retina and choroid is a rare form of inherited retinal degeneration characterized by elevated levels of the amino acid ornithine in the bloodstream due to an enzyme deficiency. Currently, studies are under way to evaluate the therapeutic efficacy of diets low in protein and arginine (an ornithine precursor), with supplemental amino acids in arresting the degeneration and improving the condition of patients with gyrate atrophy.

NUTRITIONAL STATUS ASSESSMENT

Research on nutritional status assessment includes investigations to develop and evaluate various kinds of methods useful in determining whether the requirements for essential nutrients are being met throughout the life cycle, i.e., from fetal life through infancy, childhood, adolescence, adulthood and advanced age. Studies are carried out in both normal and clinical populations, and examine: 1) biochemical, anthropometric, maturational and functional indices of nutritional status; 2) micromethods employing the latest technology and the smallest amounts to measure nutrient concentrations in various tissues and plasma; and 3) methods that improve the accuracy of dietary intake data.

Recent studies have revealed that serum growth factors, particularly the somatomedins, decrease with undernutrition and increase with refeeding in a manner correlated with the type of nutrient consumed over the course of a day. Thus, their usefulness in the assessment of nutritional status is being evaluated in the presence of diseases. These insulin-like substances are made in the liver, depend on growth, show tissue-building activity, and appear to be part of the hormonal adaptation to nutrient levels. In humans, somatomedin-C is the one of particular interest.

In one study of 28 malnourished patients, 13 who had cancer and nine who had gastrointestinal disorders, somatomedin-C levels were found to be low; ranging from 25 percent of normal in the most severely malnourished to 57 percent of normal in the least severe. In six of these patients who received nutritional therapy, somatomedin-C levels rose by more than 70 percent. In 20 patients, only somatomedin-C was correlated with recent intake of protein and calories. Other measurements of nutritional status (such as albumin and transferrin levels, lymphocyte count, skinfold thickness, muscle circumference) were not as depressed before therapy and did not rise as much during therapy. Thus, somatomedin-C levels appeared most sensitive to altered nutritional status and were quite specific to protein intake.

Intervention projects to assess dietary intake and nutritional status require data on food composition that accurately reflects the nutrients found in the food supply. Assessing the nutrient quantity and quality of diets depends upon an adequate data base for food composition. Recognizing the international need for such a data base, the International Food Composition Data System (INFOODS) was organized in 1982 as an international collaboration of organizations and persons interested in improving the amount, quality, and availabilty of food composition data. The INFOODS staff is currently focusing on the development of standards and guidelines for: 1) terminology and nomenclature used in describing foods and food components, 2) gathering of food composition data, and 3) storing and interchange of food composition data. The secretariat, which is based at the Massachusetts Institute of Technology, initiates, coordinates, and administers international task forces on specific problems, and serves as a clearinghouse of information about food composition activities around the world. The INFOODS group works with and organizes regional groups for food composition work. Four major committees, i.e., data control, terminology, information system, and the user, are responsible for special tasks of the network. Joint committees have been developed with the International Union of Nutritional Sciences to determine the nutrient value of foods, as well as to consider nomenclature and terminology relevant to food composition and the role of computers in nutrition.

The first edition of the INFOODS international directory, containing 133 food composition tables from countries around the world, has been issued and is intended as a guide for users and developers of the system. At present, the final draft of a 300 page INFOODS manual of guidelines for the production, management, and use of food composition data systems has almost been completed. The manual while primarily directed toward the techniques of gathering analytic data, also addresses the entire process of putting together food composition data base systems. INFOODS will be a comprehensive nutrient data system that will assist both researchers and policy makers in the area of diet-related health issues.

VITAMINS, MINERALS AND TRACE ELEMENTS

Investigators are continuously making attempts to better understand the metabolic functions, and therefore the specific requirements, of all essential nutrients. A large portion of this research focuses on the vitamins, minerals and trace elements, as described in some of the previous highlights.

Current knowledge about the endocrine functions, the isolation, and the chemical characterization of vitamin D_3 metabolites has led to their widespread use in treating a variety of metabolic bone diseases such as renal osteodystrophy, hypoparathyroidism, pseudohypoparathyroidism, vitamin D-resistant rickets, and osteoporosis. In addition, measurements of the vitamin D metabolites are being used to diagnose a variety of diseases, e.g., low plasma levels of 25-hydroxycholecalciferol indicate intestinal malabsorption, liver disease, biliary secretion failure or poor vitamin D nutritional status.

Vitamin D-resistant rickets (X-linked hypophosphatemia [Hyp]), a disease seen in both humans and mice, is caused by a mutant dominant gene on the X-chromosone leading to an impaired renal reabsorption of phosphate. Current therapy for X-linked hypophosphatemia in humans has been based on the theory that the renal phosphate loss is the only treatable manifestation of the disease. However, intestinal malabsorption of calcium and phosphate has been reported in children, and intestinal malabsorption of calcium associated with low intestinal calcitrol-dependent binding protein has been observed in young, rapidly growing, postweaning mice. Work with Hyp mice show normal levels of 1,25-(OH)-vitamin D receptors in the duodenum and near normal plasma levels of the hormone. Absorption of both ^{45}Ca and ^{32}P were measured by in vivo examination of isolated duodenal segments and by an oral test meal, after a 3-day infusion of varying levels of the hormone. In both instances, infused Hyp mice showed malabsorption; however, increasing doses of 1,25-(OH)-vitamin D caused a graded increase in intestinal malabsorption of both calcium and phosphorus. Although the explanation for the calcium and phosphorus malabsorption remains unclear, the data suggest that Hyp mice, at least, are not resistant to the vitamin D hormone.

In normal adult subjects, endogenous 1,25-dihydroxyvitamin D augments calcium absorption in the jejunum, ileum, and colon while it increases magnesium absorption in only the two segments of the small bowel. Thus, the selective jejunal hyperabsorption of calcium encountered in absorptive hypercalciuria could be a vitamin D-independent process.

Changes in the dietary intake of phosphorus have recently been shown to induce large, rapid, inverse and persistent changes in the serum concentration of 1,25-dihydroxyvitamin D. Phosphorus intake critically affects the serum concentration of 1,25-dihydroxyvitamin D by determining its production rate. Dietary calcium also affects the serum concentrations of this hormone; restriction of calcium increases serum concentrations of 1,25-dihydroxyvitamin D, whereas calcium supplementation induces a decrease. These changes, however, are transient and smaller than those produced by variations in dietary phosphorus.

NUTRITION AND BEHAVIOR: CENTRAL NERVOUS SYSTEM DEVELOPMENT AND FUNCTION

The nutritional status of an individual depends not only on the physiological regulation but also on the motivation controlling food intake and food selection. Regulation and motivation, in turn, are governed by a set of peripheral variables (taste, smell, gastric factors, and humoral and metabolic factors) that are integrated in the central nervous system where they may be greatly influenced by learned habits and by social, cultural and religious values. The very important role of learning and habit in food preferences and aversions is thus an essential aspect of this part of nutrition research. Research is also conducted on the ways in which excess or deficient intakes of various foods or nutrients may influence certain behaviors.

Food choices can be quantified and therefore can serve as definitive measures of outcome in the study of developmental processes during infancy, childhood and adolescence. Studies featured in other highlight sections continue to examine the factors that influence feeding behavior as it relates to the problems of obesity, anorexia nervosa and bulimia, as well as the relationship of certain nutrients to behaviors such as hyperactivity in children.

Investigations of factors that affect food selection, i.e., frequency and amount of food consumed, are also pursued in animal studies. One such study measured the choice between foods as a function of cost (work) and caloric density; cost and protein concentration; abundance, availability and macronutrient content; and imbalances of amino acids. Cost is defined as the "work," vis a vis bar press, involved in food pellet acquisition. The results of the study to date have shown that as the cost of access to a meal increases, the frequency of meals decreases and the size of meals increases in compensation. The same holds true for caloric density; increasing this variable leads to a decrease in both meal frequency and size.

Various nutrients, especially the amino acids, are known to affect central nervous system (CNS) development and function. A study of free lysine metabolism in the brain has shown that lysine is actively metabolized in the brain via the pipecolic acid pathway, and that some of its metabolites may have physiological functions as neurotransmitters and neuromodulators. Other peptides present within the CNS (cholecystokinin [CCK], thyroid-releasing hormone, and insulin) are involved in the regulation of feeding behavior, and therefore in the control of body weight. Research conducted in sheep has shown that CCK is extremely potent in suppressing feeding behavior when injected into the cerebral ventricles, whereas injections of CCK antiserum into the cerebrospinal fluid (CSF) block satiety. One hypothesis is that CCK released into the brain or possibly into the ventricular system during feeding, is transported via the CSF and acts on CNS receptors involved in the elicitation of satiety.

Additional studies on central nervous system development in rats have sought to determine whether undernutrition early in development causes abnormalities in the synthesis or structure of gangliosides and glycoproteins in the synaptic plasma membranes (SPMs). Data have shown that the offspring of rats fed either a protein-calorie-deficient diet or protein-deficient diet during lactation had a marked deficit of SPMs, which was greater in the forebrain and hippocampus than in the cortex or cerebellum.

Researchers investigating the variable response of patients with Parkinson's disease to treatment with levodopa have found that meals can reduce and even block the absorption of levodopa from the intestine. It appears that amino acids, particularly those similar in structure to levodopa, compete with the drug for absorption from the intestine into the bloodstream and for its transport from blood to the brain, and can interfere with its passage into the brain, thereby decreasing its therapeutic effectiveness. This phenomenon has even been demon-

strated when levodopa was administered intravenously to patients. Although constant infusion maintained a blood level of the drug that should have been potent, symptoms of the disease recurred or worsened in some patients a few hours after eating foods high in protein or drinking solutions containing certain amino acids. The amino acids may have blocked the levodopa from reaching the nerve centers of the brain in these patients.

Adequate transport of levodopa to the nerve centers is crucial if patients with Parkinson's disease are to regain normal movement and speech. Levodopa is the prime source of dopamine, a neurotransmitter ordinarily produced by cells in the substantia nigra portion of the brainstem. In Parkinson's disease many of these cells degenerate, consequently reducing the production of dopamine, which is needed for normal function of those areas of the brain that control motor skills. Because of levodopa's short biological half-life, even a small delay in reaching nerve centers in the brain can markedly reduce its effectiveness in controlling Parkinson's disease. Patients with Parkinson's disease, therefore, are recommended to distribute their protein intake over the day in order to reduce the interference between amino acids and levodopa.

Another research area of interest is whether sulfites added to foods invoke asthma-like reactions in particularly sensitive individuals. Studies have shown that the doses of sulfite added as preservatives in restaurant meals, wines, and medications (including asthma medications) are in fact capable of provoking reactions similar to asthma in sulfite-sensitive persons. A number of orally administered agents, particularly vitamin B_{12}, have been shown to be effective in blocking this reaction.

OBESITY

Obesity is a condition of energy imbalance resulting in excessive storage of body fat. According to the statement resulting from the Consensus Conference on the Health Implications of Obesity, held in February 1985, obesity affects about 34 million Americans. Of these, 11 million are severely obese--they are 20 percent or more above desirable body weight and have an elevated risk of developing high blood pressure, adult-onset diabetes, heart disease, certain forms of cancer, or other disorders. Recent surveys indicate that obesity is not randomly distributed throughout the population, but rather falls along socioeconomic gradients. It is most common in lower-income females and in median-income males, and is least often encountered in the affluent groups of both sexes. In addition, blacks and whites are comparably fat or lean at comparable levels of education, income, or occupation.

Investigations of the cause, prevention and cure of obesity remain important research priorities. Learning more about the antecedents of obesity in childhood is of primary concern in order to identify those individuals at high risk of becoming obese later in life and to design preventive programs to meet their needs. The natural history of obesity is being studied in thousands of individuals from infancy

through adulthood. One major finding has been that obesity in infancy does not predict obesity in adolescence or adulthood, but that obesity at age 4 or above predicts obesity in adulthood with an accuracy that increases directly with age of onset. An important preventive implication of this finding is that intervention strategies employed to achieve desirable weight would be more effectively introduced during preschool years than during infancy.

Currently, little data are available on the role that individual eating behavior plays in obesity. Some obese people are believed to have certain aberrations in eating behaviors, such as eating in binges or late at night. Until recently, such behavior and the difference in eating habits between obese and lean persons could not be accurately measured. A new device, an intraoral sensor, has recently been shown to provide an unobtrusive and accurate method for recording chewing and swallowing during a meal in patterns that indicate certain types of eating behavior. These sensors consist of piezoelectric crystals that generate an electrical current when mechanically flexed, and are mounted in a retainer which fits snugly in the roof of the mouth. Swallowing produces large amplitude deflections that last about one second, and usually occur in clusters as the subject eats a large piece of food. In contrast, chews produce low amplitude deflections, only one quarter or one eighth the magnitude of those produced by a swallow. The sensors produce distinctive patterns that vary with different foods.

This new device allows investigators to calculate the rate and duration of chewing, measure the interval between swallows, and thereby arrive at objective measurements of the rate of eating. Detailed and accurate records of oral events associated with eating are also obtained. Programs have been developed for digital conversion of the data for computer analysis. Plans are currently under way to develop a portable eating monitor with an intraoral sensor that would transmit radio frequency signals to a portable tape recorder connected to a belt or placed in a pocket. This device would record data on the frequency of eating, size of each meal, snacking behavior and other factors. Coupled with food diaries that record the specific foods eaten at each meal or snack, the recordings could provide the basis for a complete evaluation of eating patterns.

The intraoral sensor device can provide objective data on eating behaviors in obesity and other eating disorders, such as anorexia nervosa and bulimia, allowing investigators to evaluate modifications of eating behavior used as therapy. Continuous monitoring using the sensors might determine what role eating behavior may play in all of these conditions.

In studies to determine appropriate dietary treatments for obesity, it appears that protein supplementation during caloric restriction preserves total body nitrogen, and that protein status can be determined by the plasma levels of somatomedin-C. Thus, somatomedin C measurements may be important to monitor protein loss during dietary therapy of obese subjects.

Studies have recently shown that losing weight is not only easier, but also healthier, when diet is combined with exercise. In one study, women on a combined diet-exercise program lost an average of 19 pounds, almost double the weight loss of women who only dieted. The maximum heart rate of women on the combined diet-exercise program decreased from an average of 186 beats per minute to 170, compared to a decrease from 182 to 175 beats in women who only dieted. Women who lost weight by diet alone did not improve subsequent treadmill performance time, while those who exercised subsequently lasted one extra minute and one half longer on the treadmill before tiring.

Another study included one group of women who attended classes on the importance of diet and exercise in weight loss, while another group attended the same classes and was concurrently enrolled in fitness classes which included stretching, jogging, and walking briskly 45 minutes a day for 3 days a week. No significant differences were found in oxygen consumption for either group of women; however, by the end of the study blood triglyceride levels were significantly lower among the women who exercised than among those who did not exercise. Women who exercised reduced their total body fat from 41 percent of their total weight to 33 percent, compared to a reduction from 39 percent to 36 percent in women who did not exercise. The nonexercised group lost 20 percent of their weight in lean body weight, rather than in body fat.

Using a known relationship between the oxygen atoms in exhaled carbon dioxide and body water, investigators have recently developed a new method of measuring average daily energy expenditure for periods of 4 to 24 days. It allows for the estimation of energy expenditure under unrestrictive or real living conditions. The method only requires periodic urine collections so that the elimination rates of oxygen and hydrogen labeled water can be measured following the oral administration of a loading dose. Water labeled with stable isotopes of oxygen and hydrogen is given orally, and 3 to 4 hours later saliva is collected for the determination of total body water by isotope dilution methods. Urine is then collected 24 hours after the dose and again after 5 to 21 days for determination of isotope elimination rates. Because oxygen in the carbon dioxide equilibrates with the oxygen in body water, the oxygen elimination rate measures the carbon dioxide and water flux, whereas the hydrogen elimination rate measures only the water flux. The difference between the isotope elimination rates is a measure of carbon dioxide flux and, therefore, of energy expenditure. In validation studies, energy expenditures derived from the doubly labeled water method have been in good agreement with those derived from concurrent 13-day intake/balance studies for 5-day continuous respiratory gas analysis.

Numerous studies are under way on the effects of exercise on the reduction of body weight in obese women since they appear to differ from nonobese females. In one study, nonobese women appeared to increase their caloric intakes in order to compensate for their increased caloric expenditure. This phenomenon was not observed in the obese women; increased energy expenditure was not associated with increased food intake. Thus, exercise may exert an early inhibitory

effect on food intake. Further studies have been designed to control for the potentially confounding variables of limited number of subjects, self-selection of nutrients, and the immediate effect of exercise on subsequent intake.

In order to examine the effects of weight loss in obese diabetics, and the relationship of obesity to concurrent diabetes, investigators have studied the effects of weight reduction by dietary means (caloric restrictions with a protein supplement at 1.4 g/kg desirable body weight) in those more than 30 percent overweight and gastric bypass surgery in obese diabetics more than 90 pounds overweight. Both treatment methods significantly improved control of blood sugar (the average fasting glucose level fell from 287 to 168 mg/dl, and the glycosylated hemoglobin, from 11.9 to 8.2 percent). Blood glucose control was directly correlated with the amount of weight loss. In the diet group, effective control resulted from caloric restriction, even prior to significant weight loss.

Studies are under way to develop behavioral weight control programs effective for improving the long-term outcome of patients with type II diabetes. In type II diabetes, control of blood glucose is enhanced by weight reduction and diet control. In one study, patients were taught to use reflectometers to measure their blood glucose values; however, they did not use the information to make changes in their eating or exercise habits. Another study was then begun in which patients were taught to regulate their eating and exercise behaviors based on their blood glucose values. Exercises in class and at home were used to demonstrate the effect of eating and exercise on blood glucose levels. The results of this research showed no significant differences in weight loss or control of blood glucose levels between the patients who merely monitored their blood glucose values, and those who were taught to alter their diet and exercise.

The highest known prevalence of obesity has been shown to be in the Pima Indians who also appear to be insulin-resistant as well as hyperinsulinemic, and have low plasma cholesterol levels, reduced low density lipoprotein (LDL) synthesis, and a decreased incidence of cardiovascular disease. The hyperinsulinemia found in Pima children is thought to contribute to the development of obesity and diabetes in adulthood.

The factors which influence the development of obesity and its influence on other coronary heart disease risk factors are being investigated in the National Growth and Health Study (NGHS). NGHS is a long-term prospective multi-center collaborative study of black and white female children, 9-10 years of age at entry. It is designed to observe the occurrence of obesity in this cohort over a 5 year period, the predictors of transition to the obese state, the correlates of this transition, and the relationship of this transition to other cardiovascular risk factors. The study will attempt to determine whether the black-white difference observed in the development of obesity in females during pubescence is due to differences in psychosocial, socioeconomic, and/or other environmental factors; and whether these differences in the development of obesity lead to

black-white differences in other coronary heart disease risk factors, such as blood pressure and blood lipids which in turn may be associated with the higher rates of cardiovascular disease in black women. Information will be obtained from the children and their parents or caretakers. Studies on the relationship of obesity, especially in black females during and after adolescence, to lipoproteins and other factors are of interest to the Subcommittee on Cardiovascular and Cerebrovascular Diseases of the DHHS Secretary's Task Force on Black and Minority Health. The results of the NGHS will provide valuable information concerning this research area.

Studies of the free fatty acid re-esterification cycle, and of adrenoreceptor physiology in human adipose tissue have increased our understanding of systemic fuel homeostasis and control of the anatomic distribution of fat. Using a highly sensitive double-radioisotope technique, it has been documented that the percentage of newly hydrolyzed intracellular free fatty acids from triglycerides that are re-esterified drops sharply from approximately 50 percent in the fed state to under 10 percent after brief fasting. In vivo studies of intravenous infusion of large amounts of glucose to fasting subjects confirm the fact that the re-esterification cycle is active and important in fuel homeostasis in man. In vitro studies of the re-esterification cycle in adipose tissue from obese subjects, weight-stable reduced obese subjects and control subjects indicate that free fatty acid re-esterification is similar in the reduced obese and fasting, normal weight individuals. However, in the reduced obese individual adipocyte morphology is almost normal, while adipocyte number remains greater. Thus, the aggregate systemic metabolic effect of the free fatty acid/glycerol ratio may be greatly amplified.

Measurements obtained by this technique indicate that fasting is associated with site-related differential enhancement of both beta-1 (lipolytic) and alpha-2 (anti-lipolytic) receptor responsiveness and sensitivity. Beta-adrenergic responsiveness in both weight-stable men and women seems to be greater in abdominal subcutaneous tissue than in gluteal subcutaneous tissue. However, alpha-2 adrenergic responsiveness appears to be greater in the female gluteal site than in the male, which may explain the female's tendency to greater accumulation of gluteal adipose tissue. This study provides important information on the mechanisms by which the differential anatomic distribution of adipose tissue is controlled in humans; this is an important process, since some data indicate that persons who have abdominally situated adipose tissue are at greater risk factor for developing disorders such as diabetes mellitus and cardiovascular disease than those persons having equivalent degrees of adiposity in the gluteal or other regions.

Studies on the pathogenesis of obesity, its diagnosis and management include various animal models of obesity, especially the genetically obese pig and Zucker rat. From studies of the genetically obese pig, it appears that the adipocyte does indeed play a key role in determining the development of obesity; e.g., uterine factors have been shown to affect adipose tissue cell division and differentiation, and

thus play a role in obesity. This genetically obese pig model permits studies in the preobese fetal animal that can lead to the identification of specific factors that cause adipocyte abnormalities in obesity. The hypothalamic-pituitary axis is now being examined as a source of adipogenic factors.

The metabolic factors important in the etiology of genetic obesity, especially the role of adipose tissue lipoprotein lipase (LPL), are being studied in the Zucker obese rat. At all stages of development, adipose LPL activity appears to be greater in the obese Zucker rat than in the lean rats. In obese rats, swim training and exercise, as well as food restriction, increased adipose tissue LPL activity and depressed plasma insulin and triglyceride levels; all effects of exercise were transient. Exercise training improved some of the metabolic disturbance, but did not normalize adipocyte size, LPL activity, or lipolysis.

Other substances being studied for their role in the etiology of obesity in the Zucker rat include insulin and cortisone. High blood concentrations of circulating insulin, but normal or even slightly elevated blood glucose concentrations have been found in the obese rat. Recent studies of genetically obese rats have shown that even at an early age, the pancreas of obese compared to lean rats secretes substantially more insulin. However, at extremely high levels of glucose, insulin secretion is comparable in obese and lean rats. Since insulin promotes the synthesis and storage of fat, the hypersecretion of insulin at normal glucose concentrations may contribute to the development of obesity.

The role of the hormone cortisone in the development of genetic obesity has been examined in rats by removing the adrenal gland, the site of cortisone synthesis. In one study, genetically obese rats adrenalectomized at a young age before they had become obese and given varying doses of hydrocortisone, were more sensitive to hydrocortisone replacement than were lean rats in terms of weight gain, insulin and triglyceride concentrations, and size of fat stores. In the absence of cortisone replacement, the frequency and amount of food intake by the genetically obese rat was reduced. These studies confirm the importance of the adrenal gland in the alteration of fuel utilization and meal patterns, thus, the increased responsiveness to steroids may contribute to the development of obesity in the genetically obese rats.

NUTRITION AND CORONARY HEART DISEASE

Coronary heart disease (CHD) remains the number one cause of death and disability in the United States and in other industrialized nations. In November 1985, due to increasing evidence from epidemiological investigations and clinical trials that elevated blood cholesterol levels are a risk factor for coronary heart disease and that the reduction of elevated blood cholesterol can lead to a reduction in heart attacks and heart attack deaths, the NHLBI launched the National Cholesterol Education Program (NCEP).

As part of a cholesterol awareness project, periodic national surveys of physicians and the public are being conducted in order to track changes in attitudes, knowledge and behavior related to cholesterol and heart disease. In 1983, baseline surveys of the attitudes and practices of physicians and the public regarding cholesterol and coronary heart disease were conducted. These two populations will be resurveyed during the spring of 1986. The baseline physician survey was a telephone survey of 1,600 practicing physicians with specialties in general practice, family practice, internal medicine, and cardiology.

Analyses of the data indicated the following important findings: of those physicians who responded, 75 percent thought that reducing high blood pressure would have a large effect on the risk of CHD and 88 percent felt that cigarette smoking would have an effect. Only 39 percent thought that reducing elevated blood cholesterol would have a large effect on CHD risk, and 28 percent thought that reducing dietary fat would have a large effect. Approximately 80 percent of physicians reported ordering serum cholesterol measurements as part of the initial checkups of middle-age men with no evidence of cardiovascular disease or diabetes; 260-279 mg/dl was the median level of serum cholesterol indicated for dietary intervention. However, 4 percent of physicians did not use diet therapy. The median level of serum cholesterol for drug intervention was 340-359 mg/dl; however, 28 percent of physicians did not use drug therapy.

The results of the public telephone survey of a national probability sample of 4,000 adults indicated that the public who responded to the survey, similar to the physicians surveyed, placed more value on reducing blood pressure and smoking than on reducing elevated cholesterol in the prevention of CHD. However, more responders from the public survey (64 percent) expressed a stronger belief that reduced blood cholesterol would lead to prevention of CHD than did the physicians (39 percent); approximately 65 percent of the public thought that reducing dietary fat would also have a large effect on CHD risk. Approximately 25 percent of the adults had not heard of the term "high cholesterol," and of those who had heard the term, most knew of its consequences. Nearly 70 percent believed that eating less cholesterol and less fat were effective ways to lower blood cholesterol; about 50 percent knew the sources of saturated and polyunsaturated fats, and that saturated fat raises blood cholesterol levels. About 98 percent thought they had had their blood pressure checked, while only 34 percent thought they had had their cholesterol checked. Less than 5 percent of adults knew their cholesterol level.

The goal of the NCEP is contribute to reducing illness and death from coronary heart disease in the United States by reducing the number of Americans with high blood cholesterol. Through educational efforts targeted at health professionals and the public, the program aims to raise awareness and understanding about high blood cholesterol as a risk factor for coronary heart disease and the benefits of lowering cholesterol as a risk factor for coronary heart disease. The four categories of health education in which the cholesterol program approaches and activities are to be developed include: 1)

professional and patient education, 2) public education, 3) school curriculum development, and 4) worksite education. In FY 1985 a series of planning workshops were held to develop educational strategies in these areas. The NCEP also has a Coordinating Committee to address program needs and opportunities; two panels of the committee have been created to deal with the development of guidelines or recommendations for the detection, evaluation and treatment of elevated blood cholesterol; and to address the problem of laboratory standardization of cholesterol measurement levels and thus assure that practitioners receive accurate readings.

Efforts have begun to develop the educational activities of the cholesterol education program. Initially, the program is encouraging a "physician first" approach which urges physicians to have their blood cholesterol measured and to assess their own knowledge and practices relative to elevated blood cholesterol levels. In addition, programs are under way to increase the public's awareness and understanding of elevated blood cholesterol; and to stimulate people to know their blood cholesterol levels.

Recent data from the Honolulu Heart study on the 10 year incidence of CHD in relation to the population's nutrient intake indicated that men who developed CHD had a lower average intake of calories, carbohydrates, starch and vegetable protein; a higher mean intake of percentage of calories from protein, fat, saturated fatty acids, and polyunsaturated fatty acids; and a higher mean ingestion of cholesterol per 1000 calories than men who remained free of CHD. In multivariate analyses--including age, systolic blood pressure, serum cholesterol, cigarettes smoked per day, and physical activity index--carbohydrates, vegetable protein, and percentage of calories from saturated fatty acids as well as from polyunsaturated fatty acids were no longer significantly related to CHD incidence.

Similar data were published previously from the Puerto Rico Heart Health program and the Framingham study. The Puerto Rico Heart Health program included men born between 1900 and 1919, who lived in three urban and four rural districts in and around San Juan. The Framingham study, which served as a model for the Honolulu and Puerto Rico studies, began in 1948 with the examination of a sample of 5,209 adults ages 30-62 years living in Framingham, Massachusetts. Although each of the three studies was designed according to special research interests, comparable data collection systems were built in.

Upon comparing the data from these three populations, several differences were apparent. On the average, Framingham men consumed more protein, saturated fat and monounsaturated fat, sugar and alcohol than the Honolulu and Puerto Rico men. On the other hand, Framingham men consumed about the same amount of polyunsaturated fats on the average, and substantially less starch than Honolulu and Puerto Rico men. As a consequence, the average Framingham diet had a lower ratio of polyunsaturated to saturated fats, and of complex to simple carbohydrates than the diets in Honolulu and Puerto Rico. The total caloric intake was higher in Framingham men, accounting in part for their greater body weight, both absolute and relative.

In the Puerto Rico study, men who had an myocardial infarction or died of CHD, but not men with other forms of CHD, had a significantly lower intake of calories and carbohydrates than men who remained free of CHD during followup, even after the contribution of alcoholic beverages was removed. The lower intake of calories in the Puerto Rico study was primarily the result of a significantly lower intake of carbohydrates, but the intake of most nutrients was lower in those who had an MI or died of CHD. The lower intake of carbohydrates was statistically significant only for starch, buth there was also a lower intake of sugar and of "other carbohydrates" in men who developed CHD.

Other studies have shown that magnesium deficiency may be a common and underdiagnosed problem in patients with cardiac disorders. Magnesium plays important roles in osmotic pressure maintenance, enzyme activation, muscular activity, energy metabolism, nerve stability and bone formation. Magnesium deficiency occurs as a result of either decreased absorption or increased excretion, and rarely is identified as an isolated deficiency. Experimental studies and clinical observations indicate that magnesium deficiency can produce serious complications, including cardiac arrhythmias, coronary spasm, hypocalcemia, low blood potassium, changes in mental status, seizures, anorexia and weakness.

In one study, the incidence of magnesium deficiency in patients with severe cardiovascular disease was assessed by determinations of both serum magnesium (sMg) and blood mononuclear cell magnesium (mMg) concentrations. The subjects included 65 males and 39 females age 23-87 years admitted to the intensive cardiac care with acute myocardial infarction, unstable angina, congestive heart failure, uncontrolled hypertension and endocarditis. Forty-four patients had a history of cardiac arrhymthias prior to admission or had experienced arrhythmias during their stay in the CCU. Fifty-five patients were on diuretic therapy for more than three weeks prior to admission. Control subjects included 27 healthy nonalcoholic controls and 33 hypomagnesemic subjects with chronic alcoholism or malabsorption. The results of the blood samples obtained from all study participants showed that 53 percent of the CCU patients compared to the normal controls had low blood mononuclear cell magnesium (mMg) content and over 90 percent of the patients had normal sMg concentrations. Thus, mMg content may indeed be a better index of magnesium deficiency than sMg level. Magnesium levels in cardiac patients can be influenced by loop diuretics and digitalis which induce loss of magnesium, and a low magnesium content in the diet. These data suggest the need to assess magnesium intake in chronically ill patients and to consider the potential influence of medication on magnesium status.

Scientists have discovered that the omega-3 PUFAs, the principal components of fish fat which are also prevalent in some fresh green leafy vegetables, appear to have a number of health enhancing properties. Interest in the health-related roles for the omega-3 fatty acids was stimulated by epidemiological investigations carried out

in Greenland Eskimos that suggested a link between habitual ingestion of omega-3 PUFAs in the diet and the low death rates from atherosclerotic disease. The Eskimo diet consisted of 400 grams per day of meat from arctic mammals (seal and whale) and some fish. This diet resulted in a daily intake of approximately seven grams of omega-3 fatty acids, consisting largely of EPA (20:5 omega-3), and DHA (22:6 omega-3), rather than linoleic acid (18:2 omega-6), which is the predominant polyunsaturated fatty acid in the American diet. The Eskimo diet is somewhat lower in saturated fatty acids than the typical American diet.

In addition to lower rates of cardiovascular disease, the Greenland Eskimos have been shown to have a prolonged bleeding time, easy bruisability, a decreased number of platelets, and decreased platelet aggregation consistent with a decreased rate of coronary thrombosis. The Eskimos also have an increased prevalence of hemorrhagic stroke and cirrhosis of the liver, while diabetes mellitus is rare.

The relation between fish consumption and CHD was also assessed in a longitudinal study of 852 middle-age men from the town of Zutphen in the Netherlands. The average fish consumption of the Zutphen men was 20 grams per day in 1960; about two-thirds consisted of lean fish and one-third consisted of fat fish. About 19 percent of the men did not eat fish. An inverse relationship was found between fish consumption in 1960 and mortality from CHD assessed in 1980. The risk ratios for death from coronary heart disease were approximately 2.5 times lower among men who consumed either 30-44 grams, or more than 44 grams of fish per day. The average amount of EPA present in the Zutphen diet was estimated to be 0.4 grams per day. The inverse relationship between fish consumption and death from coronary heart disease was seen not only with the highest fish consumption but over the whole range of fish consumption.

In a 3 month clinical study, additional data related to the health effects of omega-3 PUFAs were obtained. Seven volunteers followed a diet with its fat derived solely from salmon oil for the first month, their normal diets in the second month, and a control diet derived solely from vegetable oils in the last month. The cholesterol content of the experimental diet and the control diet was the same. Compared to the vegetable oil diet, the fish oil diet reduced the average plasma cholesterol levels 23 percent and plasma triglyceride levels 43 percent; VLDL cholesterol levels were reduced by 50 percent and LDL cholesterol fell 20 percent in those on the fish oil diet compared to those on the control diet. Other studies have shown that the omega-3 PUFAs in the fish oil diet reduced plasma cholesterol concentrations and triglycerides by lowering the rate of synthesis of LDL and VLDL by the liver and vascular tissues. The reduced levels of LDL appeared to be the result of a decreased synthesis of LDL, rather than from an increased metabolic destruction.

One study extended the aforementioned observations in normal subjects to 20 patients with hypertriglyceridemia who were given three metabolically controlled diets: a low fat and low cholesterol (control) diet, a fish oil diet, and a polyunsaturated vegetable oil

diet. In type IIb hyperlipidemia, the fish oil diet decreased plasma cholesterol levels by 27 percent and plasma triglyceride levels changed by 64 percent, largely because of the reduction in VLDL triglyceride levels. The vegetable oil diet had a much smaller effect on VLDL cholesterol and triglyceride than the fish oil diet. LDL values were similar, but HDL cholesterol levels were higher after the vegetable oil diet. Plasma apolipoprotein changes reflected the changes in lipoprotein lipids. Significant reductions noted in apolipoprotein B and C-3 levels during the period of the fish oil diet paralleled the declines in LDL and VLDL levels.

In patients with type V phenotype, during the fish oil diet, total plasma triglyceride level decreased from 1353 to 281 mg/dl or by 79 percent; VLDL triglyceride levels decreased similarly from 1249 to 171 mg/dl. Plasma cholesterol levels dropped from 377 to 195 mg/dl; most of this decrease in total plasma cholesterol occurred as a result of marked changes in the level of VLDL cholesterol, which decreased from 251-74 mg/dl. There was a 48 percent concommitant rise in the level of LDL cholesterol from 77 to 110 mg/dl.

When the omega-6 rich vegetable oil replaced the fish oil in the diets of eight type V patients, all eight had increases in plasma triglyceride levels within 3 to 4 days. After 10-14 days of the vegetable oil diet, the mean plasma triglyceride levels rose by 198 percent and the VLDL triglyceride value increased from 171 to 550 mg/dl. The plasma cholesterol level increased from 195 to 264 mg/dl while LDL levels dropped by 28 percent. Because of more severe hypertriglyceridemia and the risk of abdominal pain typical of the type V disorder, the vegetable oil was discontinued. The question whether fish oils should be used as dietary supplements in the treatment of severe hypertriglyceridemia remains unanswered. Further studies will be required to establish the minimal effective amounts of fish oils and fish for optimal hypotriglyceridemic effects.

Thus, PUFAs from fish oils seem to be as effective as PUFAs from vegetable oils in reducing plasma total cholesterol. However, lipoprotein responses to the type of PUFA varies considerably. Unlike vegetable oils, fish oils causes a dramatic reduction in plasma VLDL and triglyceride levels particularly in patients with hypertriglyceridemia. The effects of fish oil on LDL and HDL levels however appear to be inconsistent.

The difference in chemical structure between PUFAs of the omega-3 series versus the omega-6 series appear to affect several metabolic processes related to blood platelet function and thrombosis as well as lipid metabolism. EPA may interfere with the normal metabolism and function of platelets. The release of arachidonic acid, an omega-6 fatty acid that is formed from linoleic acid, from platelet membrane phospholipids is rapidly converted to thromboxane A2, a highly potent inducer of platelet aggregation and secretion. Diets rich in fish oil fatty acids appear to decrease the content of arachidonic acid and increase the content of EPA in platelet membranes. Furthermore, platelet membrane eicosapentaenoic acid is released in response to agonists, inhibits the metabolism of

arachidonic acid, and is converted to metabolic products that themselves inhibit platelet function. Because platelets have a key role in thrombosis and are thought to promote the proliferation of arterial smooth muscle cells during atherogenesis, these effects of EPA alone might be expected to influence the biology of the arterial wall.

A second potential effect of EPA on atherogenesis is that the fish oil PUFAs alters the function of monocytes, which adhere to the arterial endothelium and migrate into the intima at early stages of hypercholesterolemia induced atherosclerosis. They are then transformed into macrophages which not only act as scavengers of plasma lipoproteins and lesion cholesterol but also probably release growth factors that stimulate the proliferation of arterial smooth muscle cells. If leukotriene B_4 influences the adherence of monocytes to the arterial endothelium as it does the adherence of neutrophils, then monocytes that contain increased amounts of EPA and show decreased production of leukotriene B_4 may not show this behavior.

Recently studies have also reported on the lipid-lipoprotein effects of oleic acid (18:1 omega-9), omega-9 being the third major family of PUFAs. The principal sources of the omega-9 series are synthesis from acetate; animal fats; and vegetable fats, particularly olive oil. One study found that in normal patients, safflower oil high in the monounsaturated fatty acid, oleic acid, is as effective as linoleic acid in lowering LDL cholesterol levels, while it seemingly reduced HDL cholesterol levels less frequently than did linoleic acid.

Obtaining information on a population of young adults is the goal of the longitudinal studies of Coronary Heart Disease Risk Factors in Young Adults (CARDIA), a prospective epidemiological investigation of the precursors and determinants of CHD risk factors and their evolution over time in a biracial cohort of young men and women (ages 18-30 years). The principal objectives of the study are 1) to measure the prevalence and distribution of risk factors in this population (i.e., lipids/lipoproteins, blood pressure, smoking, adiposity) that have been related to the development of CHD in older cohorts; and 2) to identify life styles which influence changes in risk factors. There are four clinical centers, a data coordinating center, and four laboratories to quantitate lipids, lipoproteins, and apoproteins, blood chemistries, serum cotinine and serum insulin.

Fifty-one hundred individuals will be randomly selected from the community with adequate representation of all age-race-sex specific strata. The exam protocol includes phlebotomy, blood pressure, personal and family medical history, demographic information, several psychosocial inventories including a type A/B structured interview, a quantitative food frequency dietary instrument, pulmonary function testing, anthropometry and physical activity measures as well as a grade maximal exercise test. This exam will be readministered two years later to quantify changes in life styles and risk factors that have occurred in the intervening period. The protocol has been completed and the field operations commenced in March 1985 with the

first cycle of exams scheduled to terminate in May 1986. Cycle II exams will run from March 1986 through May 1988 after which the final date editing and analysis will begin.

In attempts to identify dietary factors that affect human lipid metabolism and the clinical conditions associated with hyperlipidemias, the cynomolgus monkey, Macaca fascicularis, is a useful research model. For example, when cynomolgus monkeys are fed diets with calories from carbohydrate and fat in amounts typical of those found in human diets, subtle but significant changes occur in the balance of low and high density lipoproteins. While such changes occur in other animal models, the levels of particular dietary constituents provided must be exaggerated to reliably mimic those effects likely to occur under more normal circumstances in people. The cynomolgus monkey model is presently being integrated into research that more closely approximates these normal circumstances. Such work is focusing on the effects of alcohol, as well as varying types and levels of dietary fat on low and high density lipoprotein metabolism, and the long-term effects of dietary salt on the regulation of blood pressure in humans.

HYPERTENSION

Studies on the effects of different diets and specific nutrients in the prevention, treatment and control of hypertension are of particular research interest. The results of a collaborative study on the maintenance of blood pressure control with dietary treatment showed that weight loss or sodium restriction can retard the return of high blood pressure in patients who have achieved normal blood pressure levels through drug treatment. This dietary intervention study in hypertension enrolled 496 patients who had participated in the Hypertension Detection and Followup Program (HDFP) and whose blood pressure was controlled for up to five years by dietary intervention during the followup program. Patients in the dietary intervention group included those individual who needed to lose 10 pounds and those who were prescibed a reduction of 40 mEq of sodium. Control groups received no dietary intervention. Over 56 weeks, the patients in the dietary intervention groups were more than twice as successful as those in the control groups in maintaining normal blood pressure. High rates of success were observed among normal weight patients with mild hypertension on sodium restriction (78 percent maintained normal blood pressure), and among overweight patients with mild hypertension on weight reducing diets (72 percent).

For the estimated 40 million Americans who are treated for high blood pressure or have elevated diastolic blood pressure, this study has important implications. Should these short-term observations be confirmed in a longer period of followup, many patients who adhere to a dietary regimen to control blood pressure may be able to reduce or stop drug therapy with potential economic and health advantages. Long-term observations are needed to ascertain that the results are not temporary.

A number of other investigators are studying the mechanisms of sodium sensitivity in an attempt to identify markers for abnormal vascular and neural response to a high sodium intake. Such markers would help to identify those persons who would benefit from a low sodium diet. Epidemiological evidence indicates that some populations with low sodium intake and low blood pressure also have high potassium intakes. Several animal studies have found that potassium protects against the blood pressure elevation produced by sodium in salt sensitive rats and also reduces blood pressure in a strain of spontaneously hypertensive rats. Drug therapy is expensive and may have negative side effects; compliance is also a problem. An approach that includes increasing potassium or adjusting the sodium/potassium ratio would contribute significantly to health if such changes resulted in lowered blood pressure. Investigators are currently attempting to determine whether increasing dietary potassium to greater than or equal to 120 mEq per day or changing the sodium/potassium ratio to less than or equal to 0.7 reduces blood pressure.

Data collected from the Puerto Rico Heart Health program tested the hypothesis that a low calcium intake is related to increased blood pressure. Among urban Puerto Rican men and older rural men without baseline CHD and not taking antihypertensive medication, an inverse relationship was observed between milk consumption and definite hypertension. When data from all age and area groups were averaged, a twofold increase in hypertension was found in subgroups who drank no milk, compared to those who consumed over one quart of milk per day. Similar trends were found when an estimate of total calcium intake from food, principally milk, was used. With multivariate analysis to simultaneously consider known correlates of blood pressure, an independent effect persisted between milk consumption and blood pressure.

NUTRITION AND CANCER

A number of basic studies and clinical trials are under way investigating the role of diet and nutrition in reducing cancer risk. The identification of the possible role of specific foods or food groups in cancer prevention is a major research focus in the hope of using dietary modifications acceptable to the general public or to selected high risk groups to reduce cancer incidence. Studies of dietary fibers, retinoids, and carotenoids in food are attempting to develop better methods for the detection and quantification of the different forms of these nutrients in foods and their effects in humans. A large clinical trial is in progress to test the hypothesis that the risk of breast cancer may be reduced by changing to a low fat diet.

Fiber is a dietary component under investigation for its possible effects on disease prevention, especially colon cancer. Studies are ongoing to determine the chemical characteristics of various fiber components, to develop the appropriate methods for measuring dietary fiber, and to evaluate the effects of different forms and sources of dietary fiber components on the digestion, absorption, and bioavailability of nutrients. The various forms of fiber being

studied include cellulose, xylan, pectin, corn bran, and wheat bran. Cellulose or wheat bran have been shown to decrease digestive enzyme activity in the small intestine either by dilution of the contents, or by interfering with enzyme activity. Pancreatic enzyme activity, however, increased with the ingestion of wheat bran. In terms of fiber's effect on the bioavailability of minerals, differences may be due to variations in the fiber composition of natural fiber sources.

Studies include investigations of the effects of cellulose, xylan, pectin, and corn bran on the bioavailability of calcium, magnesium, phosphorous, iron, copper, zinc, and selenium. One study of pectin reported a decrease in B_{12} bioavailability which did not result from an interference with absorption due to calcium binding. Xylan, a bacterially digestible dietary fiber, was shown to increase liver and fecal folate levels beyond those levels provided by the diet, thereby suggesting that bacterial synthesis of folic acid was enhanced in the intestine. The effects of fiber on metabolism, therefore, may relate to the alterations in the rate of digestion and absorption of these various nutrients from the small intestine. The physiochemical effects of dietary fibers in humans are being studied to investigate the metabolic and physiological functions of the various types of dietary fiber and to elucidate their possible protective role in carcinogenesis.

Studies of vitamin A related compounds and carotenoids focus on the analysis of individual retinoids and carotenoids in the U.S. food supply. These data will aid in the interpretation of numerous epidemiological studies, especially related to lung cancer, that have shown a reduced risk associated with the consumption of foods containing large amounts of these compounds. Studies are under way of rodents, primates, and humans on the metabolism of retinoids and carotenoids in order to more fully understand their possible role in cancer prevention and treatment.

For example, in a population-based case-control study of lung cancer implemented in six high-risk areas of New Jersey, the men in the lowest quartile of carotenoid intake had 1.3 times the cancer risk of those in the highest quartile after adjusting for smoking. No increase in risk was associated with low consumption of retinol or total vitamin A. Intake of vegetables, dark green vegetables, and dark yellow-orange vegetables showed stronger associations than the carotenoid index, with the smoking-adjusted risks of those in the lowest quartiles of consumption of these food groups reaching 1.4-1.5 times the risks of those in the highest quartiles. The reduction in risk with vegetable intake was most apparent for sqamous cell carcinomas, but it extended to adenocarcinoma and most other cell types when only current and recent smokers were analyzed. Consumption of dark yellow-orange vegetables was consistently more predictive of reduced risk than consumption of any other food group or the total carotenoid index, possibly because of the high content of β-carotene, relative to other carotenoids, in this particular food group.

Analysis of the relationship of vitamin A supplementation to lung cancer showed an association of vitamin A supplements with a reduced risk (0.86) of lung cancer. No effect of daily vitamin A supplementation by duration was observed. Nor was any consistent relation noted between dose of vitamin A supplementation and outcome. Use of multiple logistic regression to control other factors, including tobacco use and level of dietary carotenoid and retinol intake, did not alter these results.

Another study attempts to identify vitamin A indicator foods, based on an index of vitamin A contribution of foods {considering frequency of consumption, portion size, and vitamin A density (IU per 100 mgK)}. Upon use of the index to rank the food items consumed in various subpopulations it appears that the relative contribution of certain fruits and vegetables to vitamin A intake varies by sex-race group, season of interview, and region of the country. Age and poverty level had little effect on the food rankings. The major contributing foods for any subpopulation included both retinol (dairy products and liver) and carotene (certain fruits and vegetables) sources of vitamin A, and items (e.g., mixed tomato dishes) not usually considered. The top 50 foods were adequate to classify correctly 80-90 percent of the individuals into low, moderate, and high consumption categories.

A national collaborative cancer prevention clinical trial entitled the Women's Health Trial is currently in progress to evaluate the effect of a low fat diet in reducing the incidence of breast cancer in women at increased risk of the disease. A feasibility study comprised of 303 women, ages 45-69 years, was conducted at three clinical centers. Potentially eligible women were recruited primarily from a cohort of women who had previously participated in the Breast Cancer Detection Demonstration Project and from health maintenance organization cohorts. Women were randomly assigned either to an intervention group who were provided dietary advice for lowering fat consumption to 20 percent of calories, or to a control group who were to continue on their usual diet containing approximately 40 percent of calories as fat. Dietary intake data were obtained by 4-day food records and a food frequency questionnaire.

The randomization procedure was effective in establishing two comparable groups. At baseline, in both the intervention and control groups, the average daily intake was 1,718 calories and 75 grams of fat, or 39 percent of calories as fat. Analysis of 4-day records collected 6 months after enrollment into the study demonstrated that the intervention group significantly reduced fat consumption with more then 88 percent of the women in this group able to achieve the goal of 20 percent of calories from fat. The mean percentage of calorie intake from fat in the control group was virtually unchanged, 38.7 percent at 6 months compared to 39.2 percent at baseline. These observations demonstrate that women can be recruited to undertake a rather stringent dietary regimen and that the intervention strategy was successful over a 6-month period. The feasibility study provides evidence strongly supporting the

practicality of conducting a full-scale trial. It is estimated that a study population of 30,000 women with a followup period of 8-10 years will be required to detect an overall reduction in breast cancer incidence of about 18 percent with a probability of 0.80. The primary endpoint is histologically diagnosed breast cancer. Secondary endpoints include cancer in a primary site other than breast or nonmelanotic skin cancer and death from any cause.

A population-based case-control study of breast cancer in young Asian-Americans is under way in Los Angeles, San Francisco, and Oahu where 630 Chinese, Japanese, and Filipino cases of breast cancer are expected to be diagnosed during 1983-1988. When Oriental women migrate to the U.S., their low rates of breast cancer rise toward American rates over a period of several generations as they adopt a more Westernized lifestyle. In this study population, diet should be sufficiently heterogeneous to permit the identification of the strong associations of diet with breast cancer risk that are presumed to exist. The study subjects are 55 years or younger so that many of their mothers, as well as they, can be interviewed about their childhood and adolesecent diet. Thus, the hypothesis that diet is operative on breast cancer risk primarily during these two periods of the life span can be evaluated. This study permits an evaluation in Asian-Americans of the standard breast cancer risk factors and an estimation of the difference in Asian and Caucasion breast cancer rates attributable to various risk factors. Several months after diagnosis, cholesterol, triglyceride, lipoprotein, tocopherol, retinol, carotenoid, selenium, and hormone determinations in blood are being made in order to study the interrelationships of ethnicity, dietary patterns, hormonal levels and disease. A number of anthropomentric measures are also included in the study design.

Basic studies of animal models for cancer have shown that supplementing the diet with omega-3 fatty acids reduces the growth of transplantable Du 145 prostatic tumors in male nude mice. Fish oil supplementation and indomethacin, a known inhibitor of the cyclooxygenase pathway of arachidonic acid, have also been shown to reduce the number of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors in the Sprague-Dawley female rat. Further, fish consumption has been suggested as a factor causing the lower breast cancer prevalence in both Greenland Eskimos and Japanese.

It has been noted in several longitudinal studies of heart disease that serum cholesterol levels were reduced among those who later developed cancer, particularly colon cancer. A cohort study of serum cholesterol levels and subsequent cancer at any site is being conducted among the 200,000 members of the Kaiser Health Plan of Northern California who participated in multiphasic screening between 1964-1972. Upon examination of the 9 most common cancers in men and the 12 most common in women, no strong or consistent relation of low cholesterol to cancer incidence was found. In addition, records from the Kaiser Health Plan of Portland are being utilized for a case-control study of colon cancer and serum cholesterol that will consider issues such as time elapsed between the cholesterol determination(s) and cancer diagnosis; medical reasons for the

cholesterol determination; relationship of multiple cholesterol values, if available; and the exact site, staging and outcome of the cancer. Of the 21 cancers examined to date, only lymphoma in men and cervical cancer had significantly elevated risks at the lowest quintile of serum cholesterol compared with risks in the highest quintile. Cancer incidence in the first 2 years after the cholesterol measurement was consistently higher among persons whose cholesterol levels were in the lowest quintile. This prospective study did not find evidence that low cholesterol increased the risk of cancer but supports the idea that preclinical cancer in some way lowers serum cholesterol.

A hospital-based case-control study of gastric cancer precursor lesions among a high-risk black population in southern Louisiana was recently completed. Dietary case-control differences indicated a protective effect associated with fruit and vegetable intake and with dietary vitamin C, but milk consumption was found to enhance risk.

An interesting pattern was observed when gastric juice parameters of subjects from Narino (Colombia) and New Orleans blacks were compared. Both populations are at high risk of gastric cancer. The values for gastric juice nitrite (resulting from nitrate reduction) were much higher in Narino samples than those from New Orleans, which may account for the much higher cancer rates in Narino. The nitrate gradient, however, ran in different directions in the two populations, which may be due to the differences in the source of nitrates. In Narino, nitrate was derived mostly from drinking water, grains and vegetable roots. In New Orleans, nitrate came mostly from fresh fruits and vegetables which apparently exert a protective effect. However, blacks who ate less fruits and vegetables had a higher frequency of dysplasia. This may be due to greater proportion of reduction of nitrate to nitrite in their stomachs compared to normal subjects, thereby enhancing the potential formation of carcinogenic N-nitroso compounds. This observation needs further study.

Nasopharyngeal carcinoma (NPC) is one of the most common cancers among Chinese residing in the southeastern provinces of China, but is rare among whites. Southern Chinese who migrated to the United States continue to show a high rate of NPC. However, their offspring who are likely to modify their traditional ways of life, display a decrease in risk for NPC. This suggests that environmental factors may be resonsible for the extraordinarily high rates of this disease in southern Chinese.

In a recently completed case-control study, any intake of Cantonese-styled salted fish during all time periods since weaning was found to be significantly associated with NPC among Hong Kong Chinese residents under age 35. The relative risk for eating Cantonese-style salted fish as one of the first solid foods during weaning was 7.5, while that for consuming the fish at least once a week compared to less than once a month at age 10 years was 37.7. Studies to characterize the carcinogenic components in this fish are currently in progress.

A death certificate-based, case-control study of colorectal cancer was carried out in three regions of Florida with high rates of in-migration from the Northeast and North Central states. The U.S. cancer mortality maps had shown that colorectal cancer mortality rates for white men and women were lower in the South by about 50 percent than in the Northeast or North Central states, a reduction that could not be explained by differences in income or population density. Close examination of the age-specific cancer mortality rates for those counties in Florida where many Northerners move at retirement, revealed that colorectal cancer rates in those counties were as low as in Southern counties of comparable population and did not rise toward the Northern rates at older ages. The characteristics of this apparent reduction in risk are being explored in order to know whether it might be due to some change in life-style such as eating more fruits and vegetables or drinking different water.

A 2-year, methodologic case-control study of colorectal cancer and diet is under way which focuses on potential diet-related biochemical markers of colorectal cancer risk, namely fecal mutagens, fecal bile acids, and fecapentaenes (a specific fecal mutagen), as well as serum nutrient levels. Case and control subjects in the study are repeatedly interviewed regarding recent diet, and multiple blood and stool samples are collected from cancer patients.

A case-control study of invasive and in situ cervical cancer was completed in five Comprehensive Cancer Centers with especially large numbers of cervical cancer patients (Philadelphia, Chicago, Miami, Birmingham, and Denver). A total of 481 invasive cases, 193 in situ cases, and 801 neighborhood controls, matched by age and race to the invasive cases, have been interviewed. This study will be the first to evaluate dietary exposures in a large number of patients with clearly invasive cervical cancer. Low intake of several nutrients--vitamin A, carotenoids, folacin, vitamin C, and vitamin E--has been postulated to increase the risk of cervical dysplasia, cervical cancer, or cancer in general. Moreover, poor nutritional status may partially explain the predominance of cervical cancer in women of low socioeconomic status. To complement the dietary interview, blood samples have been collected which will allow measurement of serum levels of retinol, carotenoids, vitamin C, folacin, and tocopherol and red blood cell folate. In addition, serum will be stored for immunologic assays of relevant infectious agents, such as herpesvirus type 2, cytomegalovirus, and chlamydia.

The International Food Composition Data System (INFOODS) was organized in 1982 as an international collaboration of organizations and individuals interested in improving the amount, quality and availability of food composition data. The work is carried out at the Massachusetts Institute of Technology, with support from NCI, NHLBI, U.S. Department of Agriculture, and the Food and Drug Administration. Considerable funding and administrative support is also provided by the United Nations University (UNU).

Progress made since INFOODS' inception 3 years ago includes a manual to improve data quality entitled "Guidelines for the Production, Management and Use of Food Composition Data System" which will be published in the near future. INFOODS is closely involved in the International Biological Reference Material Development. Work has also focused on the development of terminology and nomenclature, and information systems.

An exciting international network for the collection of food composition data is emerging with additional financial support of various foundations, important to the establishment of EUROFOODS, ASIAFOODS, and LATINFOODS. Other "FOODS" are planned such as those serving the Middle East and North Africa and Gulf states. A new international journal, the Journal of Food Composition and Analysis, will be published in 1987 as part of the INFOODS activity supported by the UNU. The journal, to be published quarterly will contain scientific papers in the area of methodology for food analysis, food component levels, and the use and processing of food composition data.

NUTRITION AND RENAL DISEASE

Research on chronic renal failure include studies of a high phosphate diet on the loss of kidney function in the rat. In one study, rats on the higher phosphate diets were shown to have higher serum calcium levels, more calcification and adverse histological changes in the kidney. This research lends support to the hypothesis that higher phosphate diets may accelerate kidney function loss through calcification in the cortical tubular cells, basement membranes and interstitium, occurring during the course of renal failure.

Preliminary information suggests that a protein-restricted, low-phosphate diet supplemented with a mixture of essential amino acids and ketoacid analogs may slow, or arrest the progression of renal insufficiency, especially if initiated early in the chronic renal failure process. Twenty-four patients with progressive renal insufficiency received a dietary prescription consisting of low phosphorus (less than 600 mg/day) and 20 to 30 grams/day of mixed-quality protein, supplemented with an essential amino acid-ketoacid mixture, at a dose of 18 grams/day (daily dose contained 1.8 grams of nitrogen). Ten of 17 patients with well-defined progression of renal insufficiency had a significantly lower rise of creatinine levels during the long-term treatment (average 20 months) than predicted; none had a faster rise than anticipated. Seven of the 17 patients began the dietary treatment before serum creatinine reached 8 mg/dl; in 6 of the 7 patients followed for an average of 22 months, creatinine remained at or below the level at the start of treatment. The nutritional status of the patients, as assessed by body weight, nitrogen balance, serum albumin, and serum transferrin levels, was well maintained.

In a long-term clinical trial of 78 patients with hypocitrate calcium nephrolithiasis, the pharmacological and physiological effects of potassium citrate therapy have been elucidated. This treatment

increased urinary citrate by stimulating citrate clearance, rather than by altering filtered load. When this drug was added to thiazide treatment, thiazide induced hypocitraturia could be readily overcome. The treatment produced remission in 74 percent of the patients, and reduced individual stone formation rate in 96 percent; for the group, stone formation rate decreased from 5.18 to 0.73 stones per year.

NUTRITION AND DENTAL DISEASES

Epidemiological and experimental studies support the hypothesis that infectious diseases and nutritional deficiencies during tooth development increase an individual's susceptibility to dental caries. Preeruptive protein calorie malnutrition and vitamin A deficiency have each been shown to increase caries development in rats. And, the posteruptive provision of foods high in refined sugar can enhance the establishment, colonization, and metabolic activity of cariogenic microorganisms in dental plaque despite the beneficial effects that may have been contributed preeruptively by a nutritious diet. Proteins can also affect plaque by providing basic amino acids that can neutralize the products of bacterial metabolism of sugars and by stimulating the rate of salivary flow. In turn, saliva can buffer acids produced by plaque bacteria or reduce the residence time of foods in the mouth thus limiting the availability of fermentable substrate to the plaque.

More epidemiological studies are needed to evaluate the relationship between human nutritional status and periodontal diseases. Overall, nutrient deficiencies affect the severity and extent of periodontal diseases by modulating the response and repair properties of the tissues. Inadequate nutrient intake could also affect the metabolism of plaque flora in the gingival crevice as well as systemic immunological responses to microbial antigens.

Xerostomia, or dry mouth, is an area of particular interest because the decrease in salivary flow or alteration in the composition of saliva can have a profound effect on oral and dental health as well as on nutritional status. Sufficient saliva is needed for the formation of a chewed mass of food to initiate the swallowing reflex. An ultrasound imaging machine is being used to diagnose swallowing disorders, in order that effective therapies can be developed.

In bulimia, an eating disorder characterized by recurrent episodes of binge eating followed by self-induced vomiting can result in gastritis, esophagitis, severe dehydration, liver function abnormality, and dental and oral-pharyngeal changes due to the chemical and mechanical effects of vomiting. In one study, a total of 16 bulimic patients and 12 controls have been examined for changes in their teeth and soft tissues (including the pharynx), enlargement of some salivary glands, elevated levels of certain digestive enzymes, and evidence of temporomandibular joint (TMJ) dysfunction (disorders of the temporomandibular joint, the hinge at the side of the head which connects the jaw to the temporal bone of the skull). All of the bulimic patients have signs and symptoms of perimylolysis, and 9 of the 16 have gingival and plaque indices indicating generalized slight mar-

ginal gingivitis and slight plaque levels. The data on teeth decayed/missing or filled, TMJ function and nutrition evaluation are inconclusive. The results of these studies are intended to provide new information, and ultimately new methods for early detection of this condition.

Some aspects of periodontal disease (alveolar bone loss) has a striking resemblance to osteoporosis. It is thought that alveolar bone loss can be used as a prediagnostic marker for frank osteoporosis and thereby minimize the advanced stages of osteoporosis. One clinical study under way to examine the relationship between osteoporosis and dental health in both postmenopausal women with and those without diagnosed osteoporosis has the following three aims: 1) to establish the existence and degree of relationship between generalized osteoporosis and dental status as evaluated by alveolar bone density and by alveolar bone loss; 2) to follow the progression of alveolar bone loss, and thus, establish the rate of bone loss; and 3) to determine the effects of different dietary and medical therapeutic regimens on dental status, and to compare those dental effects with the effects on the rest of the body. The ultimate goal of the proposed study is to develop a method of predicting who is most likely to develop osteoporosis. The working hypothesis is that the mandible is the first bone to show evidence of osteoporosis through the loss of density and through periodontal disease.

Another study has suggested that both periodontal disease and osteoporosis could be the result of a long-term dietary calcium deficiency. In this study, more cases of severe and moderate osteoporosis of the mandible and spine were found in those who had consumed virtually no milk since an early age and did not obtain their dietary calcium, compared to a group having a calcium intake of at least 1 pint of milk daily.

In various animal models alveolar bone loss appears to be induced by dietary, hormonal or traumatic means. Fluoride has been shown to inhibit bone resorption thereby suggesting that a high fluoride intake might protect against the loss of alveolar bone mass in periodontal disease. However, other data suggest that fluoride slightly increases alveolar bone loss.

The role of fluoride in the prevention and treatment of osteoporosis is complex. Several reports have indicated a reduced prevalence of osteoporosis in subjects with a high fluoride content (5-6 ppm). Such intakes stimulate both osteoblastic and osteoclastic activity, resulting in an increased rate of bone turnover. The use of fluoride in the prevention or treatment of osteoporosis may thus require very carefully controlled fluoride intakes, such that bone resorption is inhibited and bone formation enhanced.

NUTRITION AND OTHER DISEASES

Cholesterol gallstones continue to be a major concern of certain populations. In humans, supersaturation of the bile with cholesterol, commonly associated with gallstone formation, occurs more fre-

quently in obese patients with a high caloric, high-fat intake. Further, there may be associated altered lipoprotein metabolism in the form of an increased triglyceride and cholesterol synthesis and an increased very low density lipoprotein (VLDL) secretion. A hamster model that forms gallstones on an essentially fatty acid deficient diet coupled with estrogen administration is being used to study whether feeding omega-3 PUFA compared with other unsaturated fatty acids (corn oil) reduces VLDL secretion and subsequently the formation of gallstones. In addition, dietary fiber will be tested as a way to lower the cholesterol saturation of bile. The lipoprotein metabolism in this model will be compared to that of a hyporesponder (no gallstone formation) inbred strain of hamster.

In addition to the studies previously mentioned, fish oils, rich in omega-3 fatty acids, are currently receiving trials in migraine headaches, rheumatoid arthritis, asthma and other afflictions. A preliminary study in eight subjects suggests that these oils may have dramatic effectiveness in ameliorating severe migraine.

In recent studies, omega-3 fatty acids were shown to modulate immunological function and inflammation <u>in vitro</u> and in humans. Arachidonic acid is metabolized to leukotrienes in the body. Leukotrienes, in turn, are powerful inflammatory chemicals which attract white blood cells to form abscesses and constrict nonvascular smooth muscle, such as bronchial muscle to produce airway obstruction and typical asthma attacks. EPA in fish oil depresses the elaboration of leukotrienes from arachidonic acid and yields a leukotriene-like metabolite with markedly attenuated inflammatory activities. Volunteers fed fish oil capsules for 6 weeks had white blood cells that produced less leukotrienes and were less inclined to form abscesses as compared to white blood cells drawn and tested before the fish oil diet was begun and 6 weeks after its discontinuation. These results extend consideration of the epidemiological effects of fish oil-enriched diet for the first time to the function of white blood cells. However, more research is needed before dietary supplementation with fish oil can be firmly recommended in the management of established pathobiologic human conditions such as asthma or arthritis.

NEW PROGRAM ANNOUNCEMENTS, REQUESTS FOR APPLICATIONS AND REQUESTS FOR PROPOSALS IN NUTRITION

A major responsibility of the NCC is to identify areas for further research and bring them to the attention of the Institutes for the development and publication of program announcements (PAs), requests for applications (RFAs), and requests for proposals (RFPs). When areas of nutrition research are of interest to more than one Institute, including those of ADAMHA, joint PAs are often developed under the auspices of the NCC.

A PA is a formal statement of an NIH extramural research activity or of the initiation of a new or modified mechanism of support. It may describe new or modified program interests, or simply be a reminder of continuing interest.

An RFA is a formal statement which (a) invites grant applications in a well-defined scientific area to accomplish specific program purposes, (b) generally identifies only one application receipt date, and (c) indicates whether or not funds have been set aside for the competition and, if so, the amount of funds and/or the expected number of awards to be made. An RFA may be reissued as necessary.

An RFP is the government's invitation to prospective offerors to submit a contract proposal based on the terms and conditions set forth in the RFP by the statement of work that describes the nature of intended procurement. The number of contracts awarded as a result of an RFP is smaller than the number of applications funded as a result of PAs and RFAs.

In FY 1985, thirty-five nutrition announcements (2 PAs, 17 RFAs, and 16 RFPs) were published by the Institutes, compared to the 47 announcements published in FY 1984. Table I lists these PAs, RFAs, and RFPs in nutrition with the origin and date of each announcement, the type of announcement, and its title. A brief description of each announcement is included in appendix C.

TABLE I

PAs, RFAs, and RFPs in Nutrition Research and Training
Published In The NIH Guide For Grants and Contracts, FY 1985

ISSUED BY	DATE	TYPE	TITLE
NHLBI	10/3/84	RFP	Community and Cohort Surveillance Program (CCSP): Central Lipid Laboratory
NHLBI	10/12/84	RFA	Research in Nutrition and Cardiovascular Disease
NHLBI	10/12/84	RFA	Childhood Nutrition, Physical Activity and CV Health
NHLBI	10/12/84	RFA	Specialized Centers of Research in Arteriosclerosis (SCOR-A) National Research and Demonstration Centers In Arteriosclerosis
NHLBI	10/12/84	RFA	Specialized Centers of Research Concerned with Respiratory Disorders of Neonates and Children
NHLBI	10/12/84	RFA	Workplace Demonstration and Education Research in Cardiovascular Diseases
NHLBI	10/12/84	RFA	Cell Biology of the Vasculature in The Pathogenesis of Hypertension
NHLBI	10/12/84	RFA	Exercise, Stress and Atherosclerosis
NCI	10/12/84	RFA	Cooperative Agreement: Cooperative Group for Studies on Mutagens in Human Foods
NCI	10/18/84	RFP	Preclinical Toxicology of Chemopreventive Agents
NCI	11/9/84	RFA	Cancer Control Small Grants Research Program
NICHD	11/9/84	RFA	The Physiology of Lactation and the Biology of Human Milk
NHLBI	11/15/84	RFP	Longitudinal Studies on Development of Obesity in Young Black and White Females--Clinical Centers

TABLE I (cont.)

PAs, RFAs, and RFPs in Nutrition Research and Training
Published In The NIH Guide For Grants and Contracts, FY 1985

ISSUED BY	DATE	TYPE	TITLE
NICHD	11/15/84	RFP	Factors Associated with Premature Births Derived from Vital Statistics and Hospital Records Abstraction
NHLBI	12/3/84	RFP	Honolulu Heart Program
NICHD	1/15/85	RFP	Development of Methods of Analysis of Human Colostrum and Milk
NICHD	1/15/85	RFP	Animal Models for Studies of Neural Tube Defects
NIA	2/1/85	PA	Studies on Exercise Physiology and Aging
NHLBI	2/4/85	RFP	Twin Study Third Examination
NICHD	3/1/85	RFA	Cooperative Multicenter Network of Neonatal Intensive Care Units
NHLBI	3/6/85	RFP	Longitudinal Studies on Development of Obesity in Young Black and White Females--Coordinating Center
NCI	3/20/85	RFP	Case Control Study of Cancer and Drinking Water Contaminants
NCI	4/25/85	RFP	Synopsis to Review the Literature for Data Relevant to Carcinogenesis
NICHD	4/26/85	RFA	Non-Invasive Assessment of the Normality of Single Pregastrula Embryos
NCI	4/26/85	PA	National Collaborative Chemoprevention Projects
NCI	5/1/85	RFP	Support Service for the Diet, Nutrition and Cancer Program
NIDR	5/7/85	RFP	Effect of Toothbrushing with 0.4% Stannous Fluoride Gel on Periodontal Health
NCI	5/8/85	RFP	Investigations of Tumors that Occur Excessively Among Blacks

TABLE I (cont.)

PAs, RFAs, and RFPs in Nutrition Research and Training
Published In The NIH Guide For Grants and Contracts, FY 1985

ISSUED BY	DATE	TYPE	TITLE
NICHD	6/21/85	RFP	Ethnic Differences in Life Style, Psychological Factors and Medical Care During Pregnancy
NIDR	6/21/85	RFA	Differentiating Agents in Human Malignancies
NHLBI	7/9/85	RFP	The Framingham Study Physical Examination, Testing and Surveillance
NICHD	7/18/85	RFA	Cooperative Agreement on Cooperative Multicenter Program on Environmental Conditions for Nonhuman In Vitro Fertilization and Preimplantation Development
NCI	7/18/85	RFA	Cooperative Agreements for National Collaborative Chemoprevention Projects
NIA	7/18/85	RFA	Neurologic, Muscular, Perceptual and Cardiovascular Aspects of Falls and Gait Disorders in Elderly Persons
NCI	9/13/85	RFA	Studies on Novel Human Exogenous and Endogenous Retroviruses

THE CLINICAL NUTRITION RESEARCH UNITS

The establishment of the Clinical Nutrition Research Unit has been one of the most important accomplishments of the NCC. The CNRUs form the basis of a National Program in Clinical Nutrition Research. The RFA entitled "Core Grants for Clinical Nutrition Research Units (CNRUs)," published jointly by NCI, NIADDK, and NIA in January 1979, led to funding of four units in FY 1979 and three additional units in FY 1980. Because of the success of the CNRU program, the RFA was reissued to expand the program. NCI, NIADDK and NIA again participated in the revised RFA entitled "Core Grants for Clinical Nutrition Research Units," which was published in the NIH Guide for Grants and Contracts in August 1984.

In response to the RFA, there were 16 proposals submitted from which three new CNRUs were established, one supported by NCI and two by NIADDK. In FY 1985, NCI supported CNRUs at the following locations; the University of Alabama in Birmingham, Memorial Hospital for Cancer and Allied Diseases/Memorial Sloan-Kettering Cancer Center, and

Harbor UCLA Medical Center. The CNRUs supported by NIADDK are at the University of California at Davis, the University of Washington in Seattle, Vanderbilt University, the University of Wisconsin, the University of Chicago, the University of Georgia, and Columbia University. These CNRUs are designed to provide the milieu for research, training, and education through coordinated effort, intellectual stimulation, and the use of shared resources.

A CNRU is an integrated array of research, educational, and service activities that is oriented toward human nutrition in health and disease. It serves as the focal point for clinical nutrition research activities and for the stimulation of high quality research in areas such as improved nutritional support of acutely and chronically ill persons, nutritional support of the hospitalized patient, assessment of nutritional status, effects of disease states on nutritional needs, and effects of changes in nutritional status on disease. Each CNRU must consist of the following seven components: research with human subjects and populations; laboratory investigations; research training; shared facilities and research services; education programs for medical students, house staff, practicing physicians, and paramedical personnel; nutritional support services; and public information activities.

The CNRU program, now in its sixth year, has been very successful in strengthening a multidisciplinary research program in clinical nutrition and in improving the educational program for medical students as well as other health professionals. In addition, the CNRU program has provided support for the training of new clinical investigators and the development of nutrition education materials for patients and the general public.

In order to foster integration and support interactions among the ten CNRUs, NIH sponsors an annual meeting of the CNRU directors to discuss research progress and future research needs. The fifth annual meeting of CNRU directors was held in conjunction of the second Conference of Federally Supported Human Nutrition Research Units and Centers, sponsored by the Interagency Committee on Human Nutrition Research. The details of this conference are described on page 84 of this report.

One of the important outcomes of the CNRUs has been the increased visibility of nutrition programs, including opportunities for participation by medical students and fellows in research projects on nutrition problems, as well as the increased awareness of faculty of the appropriateness of a place for nutrition in the management of patients.

In FY 1985, the first CNRU developed outside of the United States was inaugurated in Valencia, Venezuela, during the II Cavendes Symposium on Clinical Nutrition. The symposium, held November 1-3, 1984, was sponsored by the Cavendes Foundation in collaboration with the University of Carabobo School of Medicine and the NCC. This CNRU, located at the university, is funded by the Cavendes Foundation and the university's school of medicine. The director of the CNRU also

attended the annual meeting of the directors of the NIH-supported CNRUs. The establishment of this CNRU exemplifies the solid foundation upon which the CNRU program is based, the interest of the scientific community in the program and the overall success that the program has experienced over the years.

NUTRITION CONFERENCES SPONSORED BY THE NIH

Each year the NIH sponsors a number of conferences on a variety of nutrition topics that reflect the current interest of the Institutes in areas of program development for nutrition research and training. Such conferences also help to expedite the transfer of nutrition technology to scientists and educators so as to assure the appropriate application of research to practice. Table II lists the 14 conferences held in FY 1985.

TABLE II
NIH SPONSORED NUTRITION CONFERENCES AND WORKSHOPS, FY 1985

INSTITUTE	DATE	TITLE
OMAR, NHLBI	12/10-12/84	Consensus Development Conference on Lowering Blood Cholesterol to Prevent Coronary Heart Disease
NCC, NIAID ILSI	2/8-9/85	Old Problems and New Directions in the Evaluation and Management of Adverse Reactions to Food and Food Additives
OMAR, NHLBI NIADDK	2/11-13/85	Consensus Development Conference on Health Implications of Obesity
NCC, NICHD ACLD	2/20/85	Genetics and Nutrition: Relevance to Learning Disabilities
NIADDK	3/17-22/85	Sixth Workshop on Vitamin D
NHLBI	3/18-19/85	National Cholesterol Education Program: Planning Workshop for Professional and Patient Education
NHLBI	4/16-17/85	National Cholesterol Education Program: Planning Workshop for Public Education

TABLE II (cont.)
NIH SPONSORED NUTRITION CONFERENCES AND WORKSHOPS, FY 1985

INSTITUTE	DATE	TITLE
NHLBI	5/7-8/85	National Cholesterol Education Program and the NHLBI Smoking Education Program: Planning Workshop for Worksite Programs
NHLBI	6/4-5/85	National Cholesterol Education Program: Planning Workshop of School-Based Education
NIADDK	6/16-21/85	FASEB Summer Research Conference on Trace Elements
NCC, National Fisheries Inst. & National Marine Fisheries Services, National Oceanic & Atmospheric Admin. DOC	6/24-26/85	Health Effects of Polyunsaturated Fatty Acids in Seafoods
NHLBI, NICHD NIADDK, FIC	8/18-23/85	13th International Congress on Nutrition
NHLBI	9/4-6/85	Recognition and Management of Coronary Heart Disease in Elderly
NHLBI	9/26-27/85	Comparative Evaluation of the Seven Statewide Coordination Projects

III.

FY 1985 OBLIGATIONS FOR NUTRITION RESEARCH AND TRAINING

DATA RETRIEVAL IN NUTRITION/HUMAN NUTRITION RESEARCH AND INFORMATION MANAGEMENT SYSTEM

In order to determine obligations for nutrition research and training, the Institutes' program staff reviews all research grants and contracts in accordance with the definition of nutrition research. Approximately 60 percent of the projects are 100 percent nutrition. For projects that are not 100 percent nutrition, the nutrition component is identified and the percentage of the overall project applicable to nutrition is then determined. The NIH has thus been able to eliminate such confusing and easily misunderstood terms as "primary/secondary," "major/minor," "nutrition related," and "direct/indirect" in referring to its nutrition program.

The analysis of the obligations of the NIH nutrition program is accomplished through the NCC office computerized data retrieval system that stores data on all the nutrition research and research training activities of the NIH. This data base is updated periodically and cross-checked against the NIH grant information and accounting system, IMPAC (Information for Management Planning, Analyses, and Coordination). This computer system has enabled the NCC office to carry out detailed analyses of the distribution by percentage of the nutrition component, support mechanism (contract, type of grant, etc.), and special interest areas. Other analyses are performed on an ad hoc basis.

For the third year, the nutrition research program is presented in accordance with the classification used by the Human Nutrition Research and Information Management (HNRIM) System. This system includes a computerized data base and data retrieval system that contains data on the nutrition research programs of the following Federal agencies: Department of Health and Human Services; U. S. Department of Agriculture; Veterans Administration; Agency for International Development; Department of Defense; and Department of Commerce-National Oceanic and Atmospheric Administration.

Nutrition projects included in the HNRIM system are classified under five major areas: I. Research in the Biomedical and Behavioral Sciences; II. Research in Food Sciences; III. Research on Nutrition Monitoring and Surveillance of Populations; IV. Research in Nutrition Education; and V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition. Research in the Biomedical and Behavioral Sciences is subclassified under three major components: A. Research on Normal Nutritional Requirements Throughout the Life Cycle; B. Diseases and Conditions; and C. Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels. The system is subsequently divided into 35 categories (In FY 1985, "Parenteral, Enteral, and Elemental Nutrition" was added as a category). Each nutrition research project is assigned at least one of the 35 classifications, and as many classifications as are needed are chosen in order to adequately identify all major nutrition aspects of the research activity being classified. The HNRIM classification system and the FY 1985 expenditures for each category are presented in appendix A. A narrative on the development of the HNRIM system can be found on page 81.

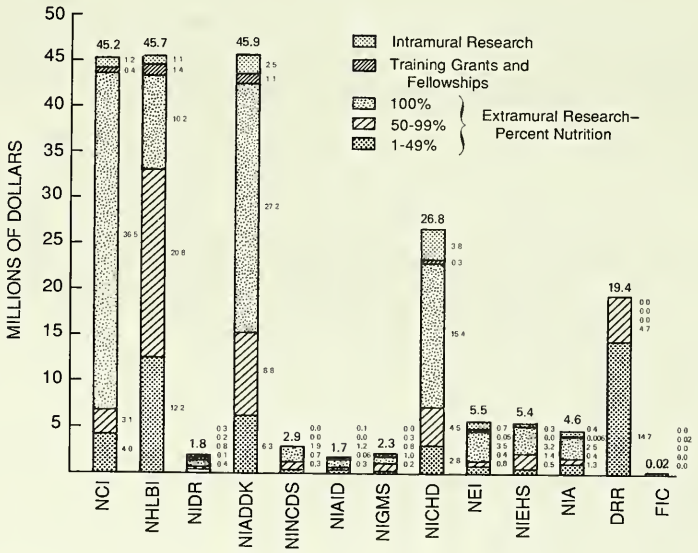
FY 1985 OBLIGATIONS FOR NUTRITION RESEARCH AND TRAINING

In FY 1985, the total NIH actual obligation in biomedical and behavioral nutrition research and training was $207,316,000. Actual obligations in nutrition by each Institute, DRR, and FIC are as follows:

NCI	45,199,000
NHLBI	45,689,000
NIDR	1,795,000
NIADDK	45,951,000
NINCDS	2,949,000
NIAID	1,679,000
NIGMS	2,307,000
NICHD	26,835,000
NEI	5,519,000
NIEHS	5,366,000
NIA	4,608,000
DRR	19,400,000
FIC	19,000

Figure 1 presents the nutrition research and training obligations of each Institute, DRR, and FIC. The total nutrition obligation by

FY 1985 EXPENDITURES OF THE NIH PROGRAM IN BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, BY B/I/D



Institute is represented by a bar divided into five segments. The lowest segment of the bar represents those grants and contracts with a nutrition component less than 50 percent of the entire grant or contract, followed by those with a nutrition component of 50 to 99 percent, and then those that are entirely (100 percent) nutrition research. The fourth segment represents training grants and fellowships, and the fifth segment represents intramural research obligations.

Figure 2 illustrates the extramural research support of the 11 Institutes and FIC, excluding DRR and nutrition training. About 59 percent of the funds are expended for projects that are entirely nutrition research; 24 percent are 50-99 percent nutrition; and the remaining 17 percent of the funds are for projects with less than 50 percent nutrition research. Between FY 1984 and FY 1985, the percentage of

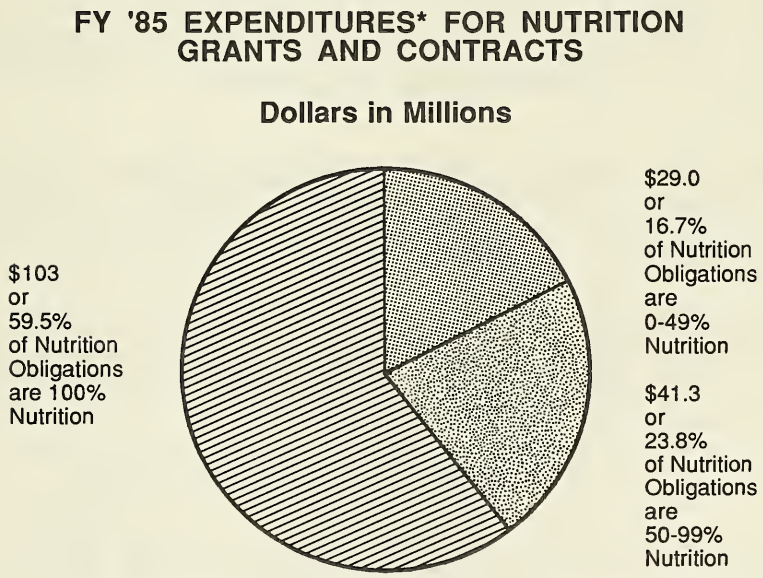


Figure 2

obligations expended for projects that are entirely nutrition decreased by one percent, while obligations for projects between 50-99 percent increased by one percent and remained the same for those less than 50 percent nutrition. Thus, the majority of the NIH program in nutrition research consists of projects where the investigators are carrying out research that is devoted entirely to nutrition.

Table III presents the FY 1985 nutrition obligations by category of support for the NIH as a whole, and appendix B contains the obligations for each Institute, DRR, and FIC (tables B-1 through B-13).

The extramural program is classified by mechanism of support into regular research grants, program projects, contracts, and centers. Clinical trials are funded by all four of these mechanisms. Research resources support, reimbursement agreements, research career development awards, new investigator research awards, and training grants and fellowships are also included in the extramural program. The intramural program consists of research projects and training (fellowships). In FY 1985, the actual obligations for extramural research, training, and manpower development accounted for $196,813,000, while intramural research and training accounted for $10,503,000. The extramural and intramural research and research training programs of the NIH were described in the FY 1984 Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training in appendix C.

Research grants support a discrete, specified, circumscribed project performed by investigator(s) in areas representing specific interests and competencies. Such research is initiated entirely by investigators outside the NIH. In FY 1985, the NIH supported 1,547 research grants in nutrition for a total obligation of $116,646,000. This category constitutes the largest single area of support in nutrition.

Program projects are also investigator initiated research, but differ from research grants in that they are awarded for the support of a broadly based, multidisciplinary, often long-term research program that has a specific major objective or a basic theme. A program project generally involves the organized efforts of relatively large groups, members of which are conducting research projects designed to elucidate various aspects or components of the major objective. In FY 1985, 74 program projects in nutrition were funded for $21,287,000.

Contracts are initiated by the agency to develop or apply new knowledge or to test, screen, or evaluate a product, material, device, or component for use by the scientific community. In FY 1985 NIH funded 154 nutrition research contracts for $15,256,000.

Centers are an additional component of agency initiated research that support any part of a full range of research and development from very basic to clinical. Centers may involve ancillary supportive activities such as protracted patient care necessary to the primary research effort. The spectrum of activities comprises a multidisciplinary approach to a specific disease entity or biomedical problem

TABLE III
National Institutes of Health
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	1,463	105,863		
	Clinical trials	84	10,783		
	Total			1,547	116,646
Program projects:	Regular	66	19,303		
	Clinical trials	8	1,984		
	Total			74	21,287
Contracts:	Regular	132	9,960		
	Clinical trials	22	5,296		
	Total			154	15,256
Centers:	Regular	43	12,327		
	Clinical trials	2	183		
	Total			45	12,510
Research Resources Support				283	19,400
Reimbursement agreements				29	3,694
Career Development Awards				87*	2,019
New Investigator Research Awards				94*	2,229
Training:	Training grants	236*	3,464		
	Fellowships	38*	308		
	Total			274*	3,772
Subtotal - Extramural					196,813
Intramural					
Projects				97	9,284
Training				46*	1,219
Subtotal - Intramural					10,503
TOTAL NUTRITION RESEARCH AND TRAINING					$207,316

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

area. In FY 1985, NIH obligations for the 45 centers with nutrition research activities were $12,510,000.

Investigator initiated research (research grants and program projects) in FY 1985 amounted to $137,933,000 (or 67 percent of all nutrition research and training obligations) whereas agency initiated research support in nutrition (contracts and centers) was $27,766,000 (or 13 percent of nutrition research and training obligations). Thus direct support for nutrition research was predominantly investigator initiated.

Clinical trials in nutrition are supported by each of the four major mechanisms discussed above--research grants, program projects, contracts, and centers. A clinical trial is defined as a scientific research activity undertaken to define the effect and value of prophylactic/diagnostic/therapeutic agents, devices, regimens, procedures, etc., applied to human subjects. The study must be prospective, and intervention of some sort must occur. The number of cases or patients depends on the hypothesis being tested, but must be sufficient to permit anticipation of a definite, statistically significant result. Phase I, feasibility, or pilot studies are excluded by definition.

FY 1985 obligations in support of 116 clinical trials involving nutrition totaled $18,246,000. These obligations constitute 9 percent of total nutrition obligations for FY 1985. The distribution of clinical trials among the four support mechanisms is displayed in table IV.

TABLE IV

SUPPORT MECHANISMS FOR CLINICAL TRIALS, FY 1985
(in thousands of dollars)

Funding Mechanism	Number of Clinical Trials	FY 1985 Expenditures
Research Grants	84	10,783
Program Projects	8	1,984
Contracts	22	5,296
Centers	2	183
TOTAL	116	18,246

Research resources support is provided by the Division of Research Resources (DRR) and NICHD. In FY 1985, $19,467,000 was devoted to this category of the NIH nutrition program with 19,400,000 supported by DRR.

DRR provides support for important resources for the performance of research in nutrition. Many investigators funded by the categorical Institutes of NIH for nutrition research use DRR's resources. DRR administers and manages five programs that serve health researchers at universities, hospitals, and research institutes throughout the United

States. These programs are the General Clinical Research Centers, Biomedical Research Support, Animal Resources, Biomedical Research Technology, and Minority Biomedical Research Support.

1. The General Clinical Research Centers Program is composed of 78 specialized centers in major hospitals throughout the United States where more than 3,000 protocols are pursued annually by clinical researchers. The program supports 80 percent of all the inpatient care costs awarded by the NIH. In addition, an extensive outpatient activity is conducted within the existing centers. The range of studies related to nutrition, on both inpatients and outpatients, includes all aspects of research in nutrition, in health and disease. Approximately 240 full-time dietary personnel are working in the General Clinical Researh Centers (GCRCs) and dietary interns spend training periods there. Most of the Centers have a diet kitchen. The program is providing support for young clinical investigators who want to pursue a career in clinical research. Several of these clinical associate physicians are involved in clinical nutrition research.

2. The objective of the Biomedical Research Support Program is to strengthen and enhance the research environment of institutions engaged in health-related research, through the use of flexible funds and local decisionmaking which enables them to more efficiently and effectively conduct their biomedical research programs. Appropriate uses of awarded funds include pilot research projects, support of new investigators, unexpected research requirements and emergencies, and central shared research resources.

3. The Animal Resources Program supports resource projects and centers that provide, or enable scientists to most effectively use laboratory animals in human-related research. The objective is accomplished through the Regional Primate Research Centers program and the Laboratory Animal Sciences program. Particular attention is given to animal resource activities that are supportive of the categorical interests of NIH.

4 The Biomedical Research Technology Program uses specialized facilities and expertise in the physical and engineering sciences to create biomedically relevant technologies and to make these technologies accessible to biomedical scientists across the country. A number of these facilities are used to support research in nutrition.

5 The Minority Biomedical Research Support Program provides funds to institutions having significant enrollments of minorities. The funds are used to provide opportunities for minorities to participate in the conduct of biomedical research, some of which is in the area of nutrition.

Reimbursement agreements are entered into between the NIH and other Federal agencies. In FY 1985, 29 such agreements were made in the area of nutrition by six Institutes, with total obligations of $3,694,000. The reimbursement agreements are listed in table V.

TABLE V

INTERAGENCY REIMBURSEMENT AGREEMENTS WITH NUTRITION RESEARCH COMPONENTS FUNDED BY NIH IN FY 1985

NATIONAL CANCER INSTITUTE
- o Chemoprevention of Epithelial Cancer by Retinoids (with Department of Energy at Brookhaven National Laboratory)
- o Research on Occupational Carcinogenesis (with National Institute of Occupational Safety and Health)
- o Epidemiological Studies of Cancer in Alaskan Natives (with Centers for Disease Control)
- o Procurement of Human Tissues (with U.S. Naval Medical Command)
- o Isotretinoin-Basal Cell Carcinoma Prevention Studies (5 agreements with U.S. Army and Naval Medical Commands)
- o Human Studies of Diet and Nutrition (with U.S. Dept. of Agriculture)
- o Cancer Prevention Awareness Survey (with Food and Drug Administration)
- o Monitoring of the Recurrent Basal Cell Carcinoma Treatment Project (with U.S. Naval Reg. Med. Center in Guam)

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
- o Atherosclerosis Project--Nonhuman Primates (with DRR)
- o CDC Lipid Standardization Program (with Centers for Disease Control
- o Services Provided to NHLBI for Nutrient Data (with U.S. Dept. of Agriculture)
- o Survey Data Performed by FDA on Coronary Primary Prevention Trial (CPPT) (with Food and Drug Administration)
- o Services Provided to NHLBI for Nutrient Composition Lab (with U.S. Agricultural Research Center)
- o Services Provided by USDA for Analysis of CPPT Study (with U.S. Agricultural Research Center)
- o International Food Composition Data System (with U.S. Dept. of Agriculture)
- o Survey of Weight Loss Behavior (with Food and Drug Administration)
- o Survey Data on Public Attitudes, Knowledge and Behavior Regarding Prevention of Coronary Heart Disease (with Food and Drug Administration)

NATIONAL INSTITUTE ON AGING
- o The NHANES I Epidemiologic Followup Survey (with National Center for Health Statistics)

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
- o Support of National Health and Nutrition Examination Survey (with National Center for Health Statistics)

TABLE V continued

INTERAGENCY REIMBURSEMENT AGREEMENTS WITH NUTRITION RESEARCH

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
o Determinants of Infant Feeding Practices (with Health Resources and Services Administration)
o Contraceptive Steroid Use from NHANES (with National Center for Health Statistics)
o XIII International Congress of Nutrition (with Food and Drug Administration)
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
o Mutagens from the Cooking of Foods (with Lawrence Livermore National Lab)
o Disposition of Inhaled Xenobiotics (with Lovelace Inhalation Toxicology Research Institute)

Career Development Awards (CDA's) and New Investigator Research Awards (NIRA's) further manpower development in nutrition research. In FY 1985, 9 Institutes supported 181 individuals at a total cost of $4,248,000 by these mechanisms.

Eighty-seven CDA awards in nutrition were supported by NCI, NEI, NHLBI, NIA, NIADDK, NIAID, NICHD, NIGMS and NINCDS for a total obligation of $2,019,000. The type and number of awards given are as follows: UPDATE

- o "Research Scientist Development Awards" support scientists, who are committed to research and need advanced research training and additional experience (4 awards).

- o "Modified Research Career Development Awards" foster the development of young scientists with outstanding research potential for careers of independent research in the sciences related to health (32 awards).

- o "Research Career Awards" enable institutions to finance positions favorable to the intellectual growth and research productivity of established investigators of high competence for the duration of their careers (2 awards).

- o "Academic/Teacher Awards" create and encourage a stimulating approach to disease specific curricula that will attract high-quality students, foster academic career development of promising young teacher-investigators, develop and implement excellent multidisciplinary curricula through an interchange of ideas, and enable the grantee institution to strengthen its existing teaching program. The academic and teacher investigator awards are

not used by all of the Institutes (37 awards).

- o "Clinical Investigator Awards" provide the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members to pursue research aspects of categorical areas applicable to the awarding unit, and aid in filling the important academic faculty gap in these shortage areas within health professional institutions of the country (9 awards).

- o "Physician Scientist Awards (Individual)" support a newly trained clinician nominated by an institution for the development of independent research skills and experience in a fundamental science (3 awards).

NIRA's are also used by the NIH as a mechanism for manpower development in nutrition. The NIRA encourages new investigators (including those who have interrupted early promising research careers) in basic or clinical science disciplines to develop their research activities within the program interests of NIH. This special grant-supported program provides funds to help bridge the transition from training status to that of established investigator. In FY 1985, 94 new investigator research awards were given for a total obligation of $2,229,000 by NCI, NEI, NHLBI, NIA, NIADDK, NIAID, NICHD, NIGMS, NIDR and NINCDS.

Training in biomedical and behavioral research is supported by NIH through national research service awards. Training grants are awarded to institutions; fellowships are awarded to individuals. In FY 1985, 236 extramural trainees in nutrition research were supported for a total of $3,464,000, and 38 fellowships awarded for a total of $308,000. Thus, total support for extramural training was $3,772,000 for the 274 trainees and fellows. (See also table VII.)

Intramural nutrition research and training was carried out by nine institutes with a total obligation of $10,503,000 of which $1,219,000 was devoted to training (fellowships) by three Institutes.

COMPARISON OF THE NUTRITION RESEARCH PROGRAM WITH THE OVERALL NIH RESEARCH PROGRAM

The entire NIH appropriation for FY 1985 was $5,152,459,000 and the nutrition obligation was $207,316,000. Thus, nutrition accounts for 4 percent of the total NIH budget. Support for nutrition research grants and program projects amounted to 5 percent of all NIH research grants and program projects, 4.1 percent of contracts, and 2.6 percent of centers. Research grants and program projects (investigator initiated research) constitute the major part of NIH support. Table VI compares the total NIH and nutrition obligations in three major components of extramural research.

TABLE VI

COMPARISON OF TOTAL NIH AND NUTRITION OBLIGATIONS IN THE THREE MAJOR COMPONENTS OF EXTRAMURAL RESEARCH, FY 1985
(in thousands of dollars)

	NIH Total		Nutrition Program	
Research grants and program projects	2,769,899	(77%)	137,933	(83%)
Contracts	375,176	(10%)	15,256	(9%)
Centers	475,968	(13%)	12,510	(8%)
TOTAL (of the three components)	3,621,043	(100%)	165,699	(100%)

As can be seen from table VI, research grants and program projects account for 77 percent of the NIH extramural research component and 83 percent of the nutrition budget. Contracts represent 10 percent for NIH and 9 percent of the nutrition program, while centers represent 13 percent for NIH as a whole and 8 percent for the nutrition program. Thus, research grants and program projects are the predominant component of both the agency and the nutrition program with such research comprising a larger percentage of the nutrition program than that of the NIH programs overall. With respect to centers, the nutrition program lags behind the NIH programs as a whole. Efforts are being made to improve this relationship.

NUTRITION RESEARCH TRAINING

The NIH supports training in biomedical and behavioral nutrition research in both the extramural and the intramural programs. Table VII shows the type and number of persons trained and the expenditures in FY 1985.

Within the extramural program, two basic mechanisms are used for nutrition training support: institutional awards and individual awards.

The institutional national research service awards, commonly called "training grants," are designed to enable institutions to make training awards to individuals selected by them for predoctoral and postdoctoral research training.

In FY 1985, out of the total NIH expenditure of $176,204,000 to train 8,793 full-time equivalent persons, $3,464,000 was expended to train 236 persons in nutrition. Thus, nutrition training accounted for 2.0 percent of the total NIH training expenditure and 3.0 percent of the total trainees supported.

The postdoctoral individual national research service awards, called "fellowships," are awarded to provide postdoctoral research training to individuals to broaden their scientific background and extend their potential for research. Out of the total NIH expenditure of $41,263,000 to support 1,831 fellows in FY 1985, the nutrition program expended $308,000 to support 38 fellows. Thus, nutrition fellowships accounted for 0.1 percent of the total NIH expenditure for fellowships and 2.0 percent of the total NIH supported fellows.

Combining training grants and fellowships, $3,772,000 was expended to support the 274 persons trained in nutrition in FY 1985. The nutrition expenditure accounted for 2.0 percent of the total NIH training expenditure and the number of trainees in nutrition accounted for 2.5 percent of the total NIH trainees.

Within the NIH intramural program, three Institutes, NHLBI, NIADDK, and NICHD, supported nutrition training of 46 scientists at an obligation of $1,219,000 in FY 1985.

Table VIII shows that whereas the number of trainees and the financial support for NIH as a whole remained relatively constant from 1978 through 1983, the number of trainees in the nutrition program doubled between 1978 and 1979, remained relatively constant until 1982, and reached its highest level in 1983. Since FY 1983, the number of trainees in nutrition as well as those supported by the NIH overall has declined with the most dramatic decline in nutrition trainees obvious in FY 1985. However comparing training in nutrition to the NIH support for training from FY 1983 to FY 1985, nutrition expenditures and number of trainees declined slightly as a percentage of total NIH training expenditures and trainees by 0.3 percent and 1.2 percent respectively: in FY 1983 nutrition training accounted for 2.3

TABLE VII
NIH TRAINING IN NUTRITION, FY 1985

Institute	M.D. Degree	Ph.D. Degree	Other Degree*	Pre-Doc	Total Number of Persons Trained	FY 1985 Obligations (in thousands of dollars)
EXTRAMURAL:						
Institute Training Grants						
NCI	4	4	2	3	13	430
NHLBI	36	83	4	10	133	1,402
NIDR	0	3	6	0	9	164
NIADDK	13	12	1	21	47	970
NIGMS	9	0	0	5	14	274
NICHD	8	6	0	5	19	218
NIA	0	1	0	0	1	6
Subtotal	70	109	13	44	236	3,464
Individual Fellowships						
NHLBI	1	5	0	0	6	6
NIADDK	1	6	1	0	8	117
NIGMS	0	1	0	0	1	15
NICHD	2	12	0	0	14	105
NEI	2	1	1	0	4	46
NIA	0	1	0	0	1	0
FIC	2	1	1	0	4	19
Subtotal	8	27	3	0	38	308
EXTRAMURAL SUBTOTAL	78	136	16	44	274	3,772
INTRAMURAL						
NHLBI	12	0	0	0	12	225
NIADDK	5	1	0	0	6	174
NICHD	10	11	7	0	28	820
INTRAMURAL SUBTOTAL	27	12	7	0	46	1,219
NIH TRAINING TOTAL	105	148	23	44	320	4,991

* Other Degree includes M.D./Ph.D, Ph.D./D.D.S., D.D.S, D.V.M., D.Sc., etc.

TABLE VIII

COMPARISON OF TOTAL NIH AND NUTRITION PROGRAM SUPPORT OF EXTRAMURAL RESEARCH TRAINING AND FELLOWSHIPS, FY 1978 - FY 1985
(in thousands of dollars)

	Total NIH				Nutrition Program			
	Training		Fellowships		Training		Fellowships	
FY	Number of Trainees	$	Number of Fellows	$	Number of Trainees	$	Number of Fellows	$
1978	9,260	117,581	1,863	26,345	130	1,956	39	463
1979	9,204	116,193	1,993	27,468	261	2,555	36	466
1980	8,878	141,719	1,786	34,669	284	3,201	51	628
1981	9,121	144,719	1,574	30,897	268	3,159	36	549
1982	8,867	123,407	1,539	27,067	307	2,419	38	415
1983	8,963	135,152	1,607	29,502	377	3,056	34	391
1984	8,908	137,307	1,606	29,155	341	2,802	35	440
1985	8,793	176,204	1,831	41,263	236	3,464	38	308

percent of the total NIH training expenditure and 4.2 percent of the total number of trainees; in FY 1984 nutrition accounted for 2.0 percent of expenditures and 3.8 percent of the number; and in FY 1985 nutrition training accounted for 2.0 percent of the total NIH training expenditure and 3.0 percent of the total number of trainees.

Since FY 1983 the number of NIH fellowships has increased with the number of fellowships in nutrition remaining relatively constant. However, nutrition expenditures for fellowships as a percent of total NIH expenditures declined by approximately 1.0 percent over the 2 years.

IV.

ACTIVITIES AND ACCOMPLISHMENTS OF THE NUTRITION COORDINATING COMMITTEE AND SUBCOMMITTEES

NUTRITION COORDINATING COMMITTEE

Many of the activities of the NCC and its two subcommittees (the Program Subcommittee and the Subcommittee on Nutrition Education) involve the transfer of the latest scientific information on various areas of nutrition research to members of the scientific community, the Congress, and the general public. Such activities help to provide the most recent scientific information on specific topics of research interest, to promote additional research in specific areas, and to alleviate confusion on nutrition topics of current debate.

Each year as part of the monthly NCC meetings, scientific seminars are presented by prominent scientists working in areas of nutrition research of current interest to the NCC members. In FY 1985, the nine seminars covered such topics as the interaction of nutrition and infection in the developing world, breast feeding and toxigenic intestinal infections: missing links in crib death?, gastric cancer and diet, natural toxicity of trace and essential elements: factors provoking the high incidence of amyotrophic lateral sclerosis and parkinsonism-dementia of Guam, aspartame; unresolved issues, childhood obesity, incidence and precursors of hypertension in young adults, dietary fat and neoplasia--the role of net energy on enhancement of carcinogenesis: effects of fat and calories on immune functions, dietary fat, carbohydrate balance and weight maintenance, and dietary fat and female sex hormones. Each of the seminars provided insight on the most recent scientific advances in the area of interest. A detailed description of each seminar presented in FY 1985 may be found in appendix D.

"Eat Well, Be Well" Videotape Series and Cookbook

In FY 1985, the "Eat Well, Be Well II" videotapes accompanied the "NIH-NCC Nutrition Research Exhibit" to a number of scientific and organizational meetings and health fairs, and were also shown as part of National Nutrition Month Activities at the NIH. The second series, which was also beamed to 225 Public Broadcasting System (PBS) television stations across the country, consists of 14 7-minute videotape segments that explain the role of nutrition in health promotion and disease prevention with nine segments featuring prominent physicians. The series, which is now also available on 16mm sound film, can also be used for nutrition instruction in primary and secondary schools, by church groups, and by any group interested in the role of nutrition in health and disease.

Plans for "Eat Well, Be Well III," which will provide nutrition information to young children in the first to fourth grade, have begun with Amram Nowak Associates, Metropolitan Life Insurance Company, NICHD and the NCC chairman. The eight segments of the series will feature nutrition information related to the concept of a balanced diet and eating foods from the various food groups, the importance of exercise, and the need to be aware of the nutrients contained in different foods in order to facilitate appropriate food choices. The series is scheduled for completion in FY 1986 and will be shown through the PBS Instructional Television Network.

Conferences Sponsored by the NCC

The mandate of the NCC includes sponsorship of conferences, workshops, and symposia in areas of nutrition research that are of concern to the Institutes. In FY 1985, the NCC participated actively in the development of two workshops and one conferences:

- The workshop on "Old Problems and New Directions in the Evaluation and Management of Adverse Reactions to Foods and Food Additives" was held February 8-9th in Orlando, Fla., and cosponsored by NIAID, International Life Sciences Institute-Nutrition Foundation (ILSI-NF), the American Academy of Allergy, and the NCC. The workshop participants critically reviewed the current information about food allergy, attempted to define food allergy, discussed ways to improve diagnostic tests used to determine prevalence of food allergy, and considered the epidemiological evidence of food allergy. The proceedings of the workshop will be published in the Journal of Allergy and Clinical Immunology.

- A workshop and round-table discussion on "Genetics and Nutrition: Relevance to Learning Disabilities" was held on February 20th in San Francisco, Calif., and cosponsored by the Association for Children and Adults with Learning Disabilities (ACLD), NICHD and the NCC. The workshop, held as part of the ACLD International Conference on Learning Disabilities, included the following topics: the genetic aspects of learning disabilities; normal intrauterine nutrition and abnormalities in nutrition that lead to fetal growth retardation and the consequences on brain growth, structure, and function; the influence of genes on learning disabilities which can be appreciated through the study of genetic syndromes; and rare hereditary diseases that require altering nutrition so as minimize the effects of the disease on the brain. The proceedings of the conference will be published as a book by the University of Illinois press.

- The joint conference on the "Health Effects of Polyunsaturated Fatty Acids in Seafoods," was held June 24-26th in Washington, D.C., and cosponsored by the National Marine Fisheries Service, National Oceanic and Atmospheric Administration, Department of Commerce; the National Fisheries Institute, and the NCC. This conference was the annual NCC conference for FY 1985.

  The two objectives of the conference were: 1) to review the research data on the health effects of polyunsaturated fatty acids in seafoods in terms of the impact of the omega-3 fatty acids on eicosanoid formation; thrombosis and atherosclerosis; lipoproteins and atherosclerosis; immunology and inflammation; and the role of docosahexaenoic acid in membrane function and metabolism; and 2) to develop a research agenda to determine the spectrum of the health effects of polyunsaturated fatty acids of seafood origin in the American diet.

  The conference brought together analytical chemists, molecular biologists, physiologists, pharmacologists, cardiologists, and

immunologists from NIH and around the world to present review papers and presentations of current research. Information presented at the conference indicated the important role of omega-3 fatty acids in the modulation of human metabolism and their potential role in the prevention and treatment of a number of diseases of public health importance, including cardiovascular disease, cancer, asthma, certain forms of arthritis, inflammatory and autoimmune processes, etc. The proceedings of the conference which will also include tables of the fatty acid composition of seafood as well as fish recipes will be published as a book by Academic Press in FY 1986.

PROGRAM SUBCOMMITTEE

In accordance with its charge, the Program Subcommittee took steps toward developing the following two joint program announcements: "Academic Award in Clinical Nutrition," and "The Biological Mechanisms of Omega-3 Fatty Acids in Health and Disease." Due to differences of the Institutes in the emphasis proposed for the Academic Award as well as in the funding mechanisms, the Program Subcommittee members decided not to pursue this announcement as a joint NCC effort. The subcommittee, however, was instrumental in the development of the latter announcement on the omega-3 fatty acids, which resulted from the conference on the "Health Effects of Polyunsaturated Fatty Acids in Seafoods." This announcement includes the research interests of the following eight NIH Institutes, namely, NIADDK, NINCDS, NIAID, NICHD, NIGMS, NEI, NIEHS, and NIA, along with the National Institute of Alcohol Abuse and Alcoholism and National Institute of Mental Health of the Alcohol, Drug Abuse and Mental Health Administration. It is scheduled for publication in the December 1985 issue of the "NIH Guide for Grants and Contracts."

The subcommittee members also provided assistance in the planning of the nutrition conferences noted above, particularly the conference on the "Health Effects of Polyunsaturated Fatty Acids in Seafoods."

Throughout the year, the subcommittee members have also provided input important for the development of NIH responses to a number of nutrition activities under way at the Department such as the proposed "Surgeon General's Report on Nutrition and Health", the "Nutrition Activities Report of the DHHS," and the "DHHS 5-Year Plan for Nutrition Research." In addition, the subcommittee members provided comments on the revised edition of the USDA/DHHS pamphlet, "Nutrition and Your Health; Dietary Guidelines for Americans." The revised guidelines were released by the two Departments in September 1985.

SUBCOMMITTEE ON NUTRITION EDUCATION

In FY 1985, in accordance with its charge and the "Guidelines for Review of NIH Nutrition Publications for the Public" the Subcommittee on Nutrition Education reviewed the following nutrition publications intended for the public: "The Pocket Fiber Guide," and the revised version of "Diet, Nutrition and Cancer Prevention: A Guide to Food Choices" developed by NCI; and "Osteoporosis: Cause, Treatment and Prevention," developed by NIADDK.

If requested by an Institute, the subcommittee members also review nutrition pamphlets intended for specific patient populations. In FY 1985, the subcommittee reviewed the pamphlet "Irritable Bowel Syndrome" developed by NIADDK.

The subcommittee is continuing its work with the GSI Cafeteria Service, through the NIH area manager, to introduce more nutritious food selections as part of the regular NIH cafeteria service. The GSI Cafeteria Service at NIH continues to feature the "Eat Well, Be Well" salad bar complete with the calorie counts of the various salad toppings at a number of the NIH cafeterias. In addition, the subcommittee also provided input to the Recreation and Welfare (R&W) Association and Occupational Medical Service (OMS) at the NIH regarding the scientific accuracy of the various nutrition programs offered to NIH employees under their aegis.

In order to avoid duplication of effort and enhance the quality of the nutrition education materials destined for the public, the subcommittee has made attempts to collect the nutrition materials prepared by the Clinical Nutrition Research Units, and to provide the CNRU directors and staff with information on nutrition publications and resources available from NIH and other agencies within the DHHS.

In FY 1985, the subcommittee began planning for the "NIH Weight Loss Competition" under the guidance of Dr. Kelly Brownell of the University of Pennsylvania, and assistance of OMS and R&W. The competition will feature a behavioral modification approach to weight loss over a twelve week period. The NCI personnel located in the Blair building will compete against the NICHD personnel in the Landow building in the "battle of the bulge". Teams will be formulated in each building to handle the details of weekly weigh-ins, behavior modification strategies, etc.

National Nutrition Month at the NIH, March 1985

For the fifth consecutive year, activities to commemorate National Nutrition Month were held on the NIH campus during March 1985. The NCC and the Subcommittee on Nutrition Education cosponsored these activities, with the cooperation of the R&W, the Occupational Medical Service (OMS), the GSI Cafeteria Service, and the NIH Fitness Center.

Since obesity is widely prevalent in the U.S. population among both children and adults, and dieting for weight control is of great interest the activities for National Nutrition Month at the NIH

emphasized the theme "Ways and Whys of Weight Control." The theme was displayed on posters featured in all of the NIH cafeterias and the ACRF Visitor's Center. The activities featured throughout the month included a special lecture on "Body Weight and Health," presented by Dr. Artemis P. Simopoulos, and scheduled viewings by the OMS of the videotape, "The Fit or Fat Test," and the slide/tape program on "Dangerous Dieting." At several of the viewings, the NIH Fitness Center personnel also presented special seminars on the importance of exercise. The OMS also began a twelve week weight loss program for employees.

Consistent with the overall theme, the GSI cafeteria service provided nutrition information, i.e., the calorie count, for the "Lean Lunch and Breakfast Bunch" specials and for the 12 salad bar toppings available at all NIH cafeterias.

The R&W and GSI cafeteria service awarded special prizes to winners of the "Nutritional Pursuit" quiz which was distributed desk-to-desk to NIH employees.

NIH-NCC Nutrition Research Exhibit

In FY 1985, the NIH-NCC Nutrition Research Exhibit was displayed and enthusiastically received at the Annual Meeting of the American Dietetic Association, held at the Convention Center in Washington D.C. Approximately 2,000 requests for the NIH nutrition publications available to the public were received at the exhibit site over the three days. The exhibit was also displayed in the Visitors Center of ACRF at the NIH during National Nutrition Month.

The freestanding exhibit, designed to be displayed at scientific meetings and health fairs, provides the scientific community, health professionals, interested consumers, and the general public with information on the NIH nutrition program. The exhibit illustrates the transfer of nutrition research from basic laboratory studies to clinical research, and the ultimate education of individuals on the role of nutrition in health promotion, disease prevention and disease treatment.

The exhibit's pamphlet, entitled "Nutrition Research at the NIH," provides descriptive information on the nutrition research programs of the 11 NIH Institutes and DRR, the names and addresses of the contact persons for the nutrition program within each Institute and DRR, as well as information on the application and review process for grants, projects, and training.

The NIH-NCC Nutrition Research Exhibit serves to illustrate the NIH commitment to nutrition research; helps to stimulate nutrition research along the lines of individual Institutes' program interests; and helps to encourage high quality applications for research projects in basic research, clinical investigation, and in the epidemiological aspects of nutrition science.

CONGRESSIONAL HEARINGS ON NUTRITION

In FY 1985, the NCC office staff provided input and was present at the hearing on the "National Nutrition Monitoring and Related Research Act of 1985, H.R. 2436," held on June 25, 1985, before the Subcommittee on Science, Research and Technology of the House Science and Technology Committee, and the Subcommittee on Department Operations, Research and Foreign Agriculture of the House Agriculture Committee. This bill was a revision of the "National Nutrition Monitoring and Related Research Act of 1984, H.R. 4684" which was discussed at the oversight hearing of June 1984. Oversight hearings on a national nutrition monitoring system have been conducted over the past 6 years. The focus of the hearing was to review Federal programs and procedures for the collection and analysis of nutritional status information, and to consider national nutrition monitoring needs and the extent to which H.R. 2436 addresses those needs. It is hoped that more effective use can be made of federal and state expenditures for nutrition monitoring and related research activities. Witnesses included representatives from scientific societies, state and local governments, public interest groups, the private sector, and the federal departments designated as chairpersons of the Intergovernment Science Board for Nutrition Monitoring and Related Research.

The Assistant Secretary for Health, DHHS, testified at the hearing on the bill and on the status of the DHHS nutrition monitoring and research activities, particularly those related to the National Nutrition Monitoring System, which is jointly implemented with USDA. The expansion of NIH-supported research from FY 1983 to 1984 on nutritional status assessment and epidemiological nutrition research was pointed out, along with the reissuance of the RFA for the support of additional Clinical Nutrition Research Units.

OFFICIAL REPORTS AND SPECIAL PRESENTATIONS ON NUTRITION

The NCC provides information on the DHHS and/or NIH nutrition research activities for inclusion in reports prepared by the General Accounting Office, as well as reports prepared by other Federal agencies. In addition to numerous special reports, the NCC office staff annually supplies data used in the publication NIH Extramural Programs, which is a compendium of the scientific programs of the NIH components that award grants, cooperative agreements and contracts. The "Program in Biomedical and Behavioral Nutrition Research and Research Training" is included in the section of the report on "Trans-NIH Research Programs."

In response to invitations from professional societies and other national and international groups interested in nutrition, the NCC staff presented the NIH nutrition research program and special nutrition topics at a number of meetings including the Sanrocco International Cancer Symposium, the conference on the Health Effects of Polyunsaturated Fatty Acids in Seafoods, the D.C. Medical Society, etc. In addition, the NCC chairman represents the NIH on the DHHS Task Force on Nutrition Objectives, the Interagency Task Force on

Implications of the Infant Formula Code for the U.S.A., and the Task Force on the Assessment of the Scientific Evidence Relating to Problems on Infant Feeding.

HUMAN NUTRITION RESEARCH AND INFORMATION MANAGEMENT SYSTEM

The NCC office staff, supported by the Division of Computer Research and Technology and in collaboration with USDA staff, through the USDA-DHHS Joint Task Force on HNRIM, under the auspices of the Joint Subcommittee on Human Nutrition Research and its successor the Interagency Committee on Human Nutrition Research, developed the Human Nutrition Research and Information Management System, a computerized data base and information retrieval system that includes data on every federally supported nutrition research project.

The development of the HNRIM system began with the work of the NCC. Since 1977, the NCC has retrieved data on NIH projects with nutrition research and training components and their nutrition expenditures, based on the definition of human nutrition research developed by the NCC. The Joint Subcommittee on Human Nutrition Research (JSHNR), operating out of the Office of Science and Technology Policy in the Executive Office of the President, expanded the NIH definition and data collection system to include the human nutrition research activities supported by participating Federal agencies, and developed a system of 34 data classification categories for human nutrition research.

In December 1981, Congress mandated the Secretaries of Agriculture and Health and Human Services to formulate a plan for a Human Nutrition Research and Information Management System. Section 1427 of the National Agricultural Research, Extension and Teaching Policy Act of 1977 (7 U.S.C.-3177), as amended by Section 1425 of the National Agricultural Research, Extension, and Teaching Policy Act Amendments of 1981 (Title XIV of P.L. 97-98) provides as follows:

> HUMAN NUTRITION RESEARCH AND INFORMATION MANAGEMENT SYSTEM
> Section 1427. The Secretary [of Agriculture] and the Secretary of Health and Human Services shall formulate and submit to Congress, within one hundred and eighty days after the date of enactment of this section, a plan for a human nutrition research management system. This system shall be based on on-line data support capability allowing for fiscal accounting, management, and control of cross-agency human nutrition research activities. The plan shall provide for management activities of all agencies managing funds for human nutrition research activities under existing authorities and contain recommendations for any additional authorities necessary to achieve a human nutrition research management system.

The Secretaries transmitted the plan to the Congress in July 1982. DHHS and USDA formed the joint task force on HNRIM, under the aegis of the JSHNR, which was charged with: 1) reviewing the JSHNR data classification system; 2) defining the elements of the computer

system; and 3) implementing the computer system. The task force reviewed and made slight modifications to the JSHNR classification system and developed a detailed database. In FY 1985, the task force decided to add another category to the existent 34 categories included in the system, i.e., "Parenteral, Enteral and Elemental Nutrition" (code 35), and to give new codes to the special interest areas (codes 51-56) specific only to NIH. The task force also prepared the third annual progress report on HNRIM for submission to the Congress.

The HNRIM system requires that each participating agency (at present DHHS, USDA, VA, AID, DOD, and DOC-NOAA) assemble and submit its own data; data from all participating agencies are combined into the HNRIM data base. The database is updated quarterly, but can be updated more frequently if the need arises. The system provides convenient access to information on human nutrition research and research training activities supported in whole or in part by the Federal Government. Fiscal data are limited to actual obligations (expenditures) by the originating Federal agency for the fiscal year in question and do not include state or private support. Federal pass-through funds are reported by the initiating agency. The information contained on projects in the data base includes: project identifier numbers, principal investigator, performing organization name and address, project title, sponsoring organization, congressional district, fiscal year, total funding, percent nutrition, nutrition funding, start data, nutrition classification categories, and a narrative description (abstract).

The HNRIM system permits online search of any field, including the full text of the narrative. Online access to over 4,000 nutrition research projects supported by the Federal Government is available through the HNRIM system. Plans are in progress to make the system available to the public for purchase through the National Technical Information Service in FY 1986.

DHHS RESEARCH INITIATIVE IN NUTRITION (DRIN)

In FY 1979, the NIH was designated as the sponsoring agency to develop the Nutrition Research Initiative, one of the DHHS Health Research Initiatives designed to focus on selected problem areas where mission needs of several DHHS agencies coincide with significant scientific opportunity. The agencies designated as cosponsors of the initiative were: NIH, ADAMHA, FDA, CDC, NCHS, and HRSA. The NIH-NCC chairman was designated as the coordinator for developing the initiative.

The purpose of the nutrition initiative is to develop within the DHHS a more comprehensive and effective program of nutrition research and training to strengthen support of related missions. The principal thrust is to reinforce a coherent research program and to extend the growing trans-Institute cooperation in nutrition research to other DHHS agencies. A committee with members from the six agencies that conduct or support nutrition research and training has been given the task to develop a cohesive program for the Department in order to best carry out this initiative in nutrition research. This committee has the following responsibilities:

- o Review and comment on the plans, execution, and results of research efforts, in order to refine and strengthen the Department's nutrition program;

- o Coordinate research stemming from the obesity program, the CNRU's, nutrition research training and manpower development programs, and participation in the Interagency Committee on Human Nutrition Research;

- o Provide information and advice on the nutrition research program to the directors of the agencies involved, to the Office of the Assistant Secretary for Health, and to the Office of the Secretary;

- o Continuously evaluate research data and provide advice for the development of nutrition education materials for the public; and

- o Plan and arrange for conferences, workshops, consensus development exercises, and reports as appropriate.

Again in FY 1985, the agencies of DRIN provided comments on the Department's "5-Year Plan for Human Nutrition Research and Training," which will be included in the "5-Year Federal Plan for Human Nutrition Research and Training" being developed by the Interagency Committee on Human Nutrition Research (ICHNR). NIH was assigned the lead responsibility for the coordination and development of the Public Health Service (PHS) portion of the plan.

INTERAGENCY COMMITTEE ON HUMAN NUTRITION RESEARCH

The Interagency Committee on Human Nutrition Research, which succeeded the Joint Subcommittee on Human Nutrition Research in June 1983, is cochaired by the Assistant Secretary for Science and Education, USDA, and the Assistant Secretary for Health, DHHS, and consists of representatives from DHHS; USDA; White House Office of Science and Technology Policy; Department of Commerce, National Oceanic and Atmospheric Administration (DOC/NOAA); Department of Defense (DOD); International Development Cooperative Administration, Agency for International Development (IDCA/AID); National Science Foundation (NSF); the Veterans Administration; and the National Aeronautics and Space Administration (NASA). The NCC Chairman serves as one of the DHHS representatives to the ICHNR.

The major responsibility of the ICHNR in FY 1985 was the completion of the "5-Year Federal Plan for Human Nutrition Research and Training," which was prepared in response to the request of the Office of Science and Technology Policy and the Congress. The purpose of the plan is to propose areas of nutrition research for special Federal attention and to assist in the development of a research strategy that will support Federal activities to maintain, improve and monitor the public's health and nutritional status. The plan was published in March 1986.

In FY 1985, the ICHNR sponsored the second Conference of Federally Supported Human Nutrition Research Units and Centers, held January 14-15, 1985, in Chevy Chase, Maryland. Highlights of the meeting included in-depth presentations on two specific topics of interest: the use of stable isotopes in nutrition research, and methods of body composition measurements. The studies presented covered such topics as mineral requirements and metabolism, energy expenditure, food composition and nutrient bioavailability, effects of exercise, protein metabolism, anthropometrics, infrared interactions, impedance, plethysmography, stable isotopes, densitometry, conductivity, and in vivo neutron activation. A report on the conference is published (American Journal of Clinical Nutrition 43:325-329, 1986).

V.
APPENDICES

APPENDIX A

HNRIM CLASSIFICATION SYSTEM
AND
FY 1985 NIH EXPENDITURES BY HNRIM CATEGORY AND SPECIAL INTEREST AREA

HNRIM CLASSIFICATION SYSTEM
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FY 1985 NIH EXPENDITURES BY HNRIM CATEGORY AND SPECIAL INTEREST AREA

The development of the HNRIM system began with the work of the NCC. Since 1977, the NCC has retrieved data on NIH projects with nutrition research and training components and their nutrition expenditures, based on the definition of human nutrition research developed by the NCC. The Joint Subcommittee on Human Nutrition Research, operating out of the Office of Science and Technology Policy in the Executive Office of the President, expanded the NIH definition and data collection system to include the human nutrition research activities supported by participating Federal agencies, and developed a system of 34 data classification categories for human nutrition research. The FY 1985 NIH nutrition research program is presented in accordance with this classification system which is used by the Human Nutrition Research and Information Management (HNRIM) System. This year another category of "Parenteral, Enteral, and Elemental Nutrition" was added as code 35 under Section I, subsection B, and the NIH Special Interest Areas were assigned codes 51-56.

I. Research in the Biomedical and Behavioral Sciences

A. Research on Normal Nutritional Requirements Throughout the Life Cycle

The following five categories are included because of the importance to health promotion of establishing normal nutritional requirements throughout the life cycle, and the differing needs of individuals at various stages of the life cycle.

Research activities relevant to normal nutrition at specific stages of the human life cycle should be assigned to classifications 1-5.

1. Maternal Nutrition

2. Infant and Child Nutrition (0-12 years)
   (includes the low birth weight infant)

3. Adolescent Nutrition (13-18 years)

4. Adult Nutrition (19-65 years)

5. Nutrition of the Elderly (65+ years)

B. Diseases and Conditions

Research on the role of nutrition in the prevention, amelioration, and treatment of diseases and conditions should be assigned to categories 6-16. Because of the importance of appropriate nutritional support of the patient in the treatment of disease, the category of "parenteral, enteral and elemental nutrition" has been added in this subsection as code 35.

6. Cardiovascular Disease and Nutrition

7. Cancer and Nutrition

8. Other Diseases and Nutrition
   (e.g., osteoporosis, diabetes, etc.)

9. Trauma (Including Burns) and Nutrition

10. Infection--Immunology and Nutrition

11. Obesity, Anorexia, and Appetite Control

12. Genetics and Nutrition

13. Nutrition and Function
    (Includes mental, psychomotor, and work performance; environmental stress)

14. Nutrient Interactions
    (Includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)

15. Other Conditions and Nutrition

16. Nutritional Status
    (Includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

35. Parenteral, Enteral, and Elemental Nutrition

C. Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels

Categories 17-25, 14, and 27 classify research by nutrient variables; these categories should be used to indicate the nutrient variables in research classified elsewhere; and classify biochemical, subcellular, cellular, and animal research, such as studies of nutrient mechanisms and metabolism not related to specific diseases, conditions, or stages of the life cycle.

17. Carbohydrates

18. Lipids (Fats and Oils)
    (Includes essential fatty acids, lipo- and apoproteins)

19. Alcohols
    (Includes ethanol, sorbitols, and other alcohols used as components in synthetic and semisynthetic foods)

20. Proteins and Amino Acids
(Includes essential as well as nonessential amino acids such as taurine and carnitine)

21. Vitamins
(Includes vitamin A, C, B_6, B_{12}, D, E, K, thiamin, riboflavin, niacin, folacin, biotin, and pantothenic acid)

22. Minerals and Essential Trace Elements
(Includes calcium, phosphorus, magnesium, iron, zinc, iodine, copper, manganese, fluoride, chromium, selenium, and molybdenum)

23. Water and Electrolytes
(Includes sodium, potassium, and chloride)

24. Fiber

25. Other Nutrients in Food
(Such as cobalt, nickel, vanadium, silicon, tin, arsenic, cadmium, choline, lecithin and various growth factors)

*14. Nutrient Interactions
(Includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)

*27. Bioavailability of Nutrients
(Includes methods for the determination of bioavailability of nutrients)

II. Research in Food Sciences

Categories 26-29 should be used for research in the nutritional aspects of food sciences.

26. Food Composition
(Includes nutritional quality, nutrient content, and research on methods of analysis for nutrients and fiber)

27. Bioavailability of Nutrients
(Includes methods for the determination of bioavailability of nutrients)

28. Effects of Technology on Acceptability and Nutritional Characteristics of Foods and Diets
(Includes the beneficial and adverse effects of varietal and species differences, harvest and post-harvest

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* This category is listed here to indicate that it may also be applicable to research on Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels (Class I.C).

technology, retail food practices, food processing, handling, preservation, and home cooking.)

29. Other Research in Food Sciences

III. Research on Nutrition Monitoring and Surveillance of Populations

30. Food Consumption Surveys
(Includes research on methods for determination of food consumption and its trends, and research utilizing data derived from such surveys.)

31. Studies of Dietary Practices, Food Consumption Patterns, and Their Determinants.

**16. Nutritional Status
(Includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

IV. Research in Nutrition Education

Categories 32-33 encompass research in nutrition education.

32. Studies on Methods for Informing and Educating the Public About Nutrition, Health, and Dietary Practices and for Countering Nutrition Misinformation
(Includes studies on methods for informing and educating professionals in these areas.)

33. Other Research in Nutrition Education

V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition

34. Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition.

The following table indicates the NIH nutrition research support in the 35 HNRIM classification categories along with the number of grants and contracts. The column labeled "percent of total" represents the funds expended in a given category in relation to total expenditures for nutrition research and research training, which for FY 1985 amounted to $207,316,000. It should be pointed out that a grant or contract may appear in more than one category. For example, a project on maternal PKU may appear under maternal nutrition and under genetics. Thus, the total expenditures in the 35 categories are larger than the sum of $207,316,000. It should be

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** This category is listed here because it may also be applicable to Nutrition Monitoring and Surveillance of Populations.

TABLE A-1

FY 1985 NIH EXPENDITURES
IN THE 35 HNRIM CLASSIFICATION CATEGORIES

Nutrition Research Classification Code	Area	Number of Grants and Contracts	Expenditure* (in thousands of dollars)	Percent of Total**
1.	Maternal Nutrition	152	12,598	6
2.	Infant and Child Nutr.	367	33,338	16
3.	Adolescent Nutrition	60	7,434	4
4.	Adult Nutrition	48	5,328	3
5.	Nutr. of the Elderly	113	9,141	4
6.	Cardiovascular Disease and Nutrition	474	53,686	26
7.	Cancer and Nutrition	591	48,821	23
8.	Other Diseases and Nutr.	364	35,253	17
9.	Trauma (Burns) and Nutr.	29	1,795	1
10.	Infection, Immunology, and Nutrition	118	8,960	3
11.	Obesity, Anorexia, and Appetite Control	262	27,180	10
12.	Genetics and Nutrition	267	31,387	12
13.	Nutrition and Function	229	19,721	7
14.	Nutrient-Nutrient/Drug/ Toxicant Interactions	316	28,664	14
15.	Other Conditions & Nutr.	373	35,308	17

(TABLE A-1 continued)

Nutrition Research Classification Code	Area	Number of Grants and Contracts	Expenditure*	Percent of Total**
16.	Res. on Nutr. Status	318	29,769	14
17.	Carbohydrates	139	12,013	6
18.	Lipids (Fats and Oils)	473	56,077	27
19.	Alcohols	39	4,261	2
20.	Proteins and Amino Acids	277	26,263	13
21.	Vitamins	500	49,741	24
22.	Minerals & Trace Elements	280	27,751	13
23.	Water and Electrolytes	141	19,430	9
24.	Fiber	33	7,293	3
25.	Other Nutrients in Food	50	5,657	3
26.	Food Composition	44	4,342	2
27.	Bioavailability	75	11,048	5
28.	Effects of Technology on Foods and Diets	10	697	0
29.	Other Res. In Food Sci.	18	664	0
30.	Food Consumption Surveys, R&D	22	1,399	1
31.	Research on Dietary Practices, Food Consumpt., etc.	210	30,250	15
32.	Methods for Educating & Informing the Public	80	13,590	6
33.	Other Research in Nutr. Ed.	15	587	0

(Table A-1 continued)

Nutrition Research Classification Code	Area	Number of Grants and Contracts	Expenditure*	Percent of Total**
34.	Effects of Govt. Policy & Socioeconomic Factors	4	84	0
35.	Parenteral, Enteral, and Elemental Nutrition	81	8,184	4

*A grant or contract may be assigned to more than one of these areas.

**The total expenditure of the NIH nutrition program in FY 1985 was $207,316,000.

noted that while NIH nutrition research encompasses all 35 classification categories, by far the largest component of NIH nutrition research is concentrated in area I, Research in the Biomedical and Behavioral Sciences.

In addition to the 35 HNRIM categories, there are 6 areas of particular scientific or political interest to NIH. Due to scientific progress and research emphasis in the area of parenteral and enteral nutrition by various Federal agencies, this NIH special interest area became HNRIM code 35, while clinical trials, an important area to the NIH program, was added as an NIH special interest area. In FY 1985, the six "special interest areas" are: nutrition and prevention of disease, international nutrition research, epidemiological research in nutrition, nutrition education for professionals, and nutrition education for public, and clinical trials. Codes 51-56 have been assigned to the special interest areas, however they are applicable only to NIH grants. The number of grants and contracts, the FY 1985 expenditures for these grants and contracts, and the percentage that these expenditures are of the total NIH nutrition program are displayed in the following table.

TABLE A-2

NIH FY 1985 EXPENDITURES IN SPECIAL INTEREST AREAS
IN NUTRITION RESEARCH AND EDUCATION

Nutrition Rsch. Classif. Code	Special Interest Area	No. of Grants or Contracts*	Expenditure* (in thousands of dollars)	Percent of Total**
51.	Prevention of Disease	1,208	119,591	58
52.	International Research	53	5,568	3
53.	Epidemiological Research	222	28,219	14
54.	Educ. for Professionals	85	2,139	1
55.	Education for the Public	16	7,462	4
56.	Clinical Trials	126	19,512	9

*A grant or contract may be assigned to more than one of these areas.

**The total expenditure of the NIH nutrition program in FY 1985 was $207,316,000.

APPENDIX B

FY 1985 NUTRITION EXPENDITURES OF THE 11 INSTITUTES, DIVISION OF RESEARCH RESOURCES, AND FOGARTY INTERNATIONAL CENTER

TABLE B-1

National Cancer Institute
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	406	23,098		
	Clinical trials	40	3,950		
	Total			446	27,048
Program projects:	Regular	14	6,149		
	Clinical trials	2	387		
	Total			16	6,536
Contracts:	Regular	48	3,475		
	Clinical trials	5	2,727		
	Total			53	6,202
Centers:	Regular	4	1,005		
	Clinical trials	0	0		
	Total			4	1,005
Research Resources Support				0	0
Reimbursement agreements				13	2,040
Career Development Awards				4*	272
New Investigator Research Awards				17*	453
Training:	Training grants	13*	430		
	Fellowships	0*	0		
	Total			13*	430
Subtotal - Extramural					43,986
Intramural					
Projects				7	1,213
Training				0*	0
Subtotal - Intramural					1,213
TOTAL NUTRITION RESEARCH AND TRAINING					$ 45,199

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-2

National Heart, Lung, and Blood Institute
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item	Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural				
Research grants: Regular	226	25,151		
Clinical trials	11	2,451		
Total			237	28,602
Program projects: Regular	14	5,083		
Clinical trials	0	0		
Total			14	5,083
Contracts: Regular	23	1,096		
Clinical trials	15	2,114		
Total			38	3,210
Centers: Regular	9	5,009		
Clinical trials	1	67		
Total			10	5,076
Research Resources Support			0	0
Reimbursement agreements			9	491
Career Development Awards			31*	528
New Investigator Research Awards			17*	169
Training: Training grants	133*	1,402		
Fellowships	6*	6		
Total			139*	1,408
Subtotal - Extramural				44,567
Intramural				
Projects			15	897
Training			12*	225
Subtotal - Intramural				1,122
TOTAL NUTRITION RESEARCH AND TRAINING				$ 45,689

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-3

National Institute of Dental Research
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	11	571		
	Clinical trials	0	0		
	Total			11	571
Program projects:	Regular	1	109		
	Clinical trials	0	0		
	Total			1	109
Contracts:	Regular	5	463		
	Clinical trials	0	0		
	Total			5	463
Centers:	Regular	1	209		
	Clinical trials	0	0		
	Total			1	209
Research Resources Support				0	0
Reimbursement agreements				0	0
Career Development Awards				0*	0
New Investigator Research Awards				1*	14
Training:	Training grants	9*	164		
	Fellowships	0*	0		
	Total			9*	164
Subtotal - Extramural					1,530
Intramural					
Projects				5	265
Training				0*	0
Subtotal - Intramural					265
TOTAL NUTRITION RESEARCH AND TRAINING					$ 1,795

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-4

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985, BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	426	30,961		
	Clinical trials	16	2,839		
	Total			442	33,800
Program projects:	Regular	13	3,146		
	Clinical trials	0	0		
	Total			13	3,146
Contracts:	Regular	2	207		
	Clinical trials	0	0		
	Total			2	207
Centers:	Regular	12	4,027		
	Clinical trials	0	0		
	Total			12	4,027
Research Resources Support				0	0
Reimbursement agreements				0	0
Career Development Awards				23*	609
New Investigator Research Awards				21*	523
Training:	Training grants	47*	970		
	Fellowships	8*	117		
	Total			55*	1,087
Subtotal - Extramural					43,399
Intramural					
Projects				31	2,378
Training				6*	174
Subtotal - Intramural					2,552
TOTAL NUTRITION RESEARCH AND TRAINING					$ 45,951

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-5

National Institute of Neurological and Communicative Disorders and Stroke
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985, BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	29	2,397		
	Clinical trials	1	62		
	Total			30	2,459
Program projects:	Regular	2	173		
	Clinical trials	1	27		
	Total			3	200
Contracts:	Regular	1	0		
	Clinical trials	0	0		
	Total			1	0
Centers:	Regular	1	0		
	Clinical trials	0	0		
	Total			1	0
Research Resources Support				0	0
Reimbursement agreements				0	0
Career Development Awards				1*	26
New Investigator Research Awards				6*	264
Training:	Training grants	0*	0		
	Fellowships	0*	0		
	Total			0*	0
Subtotal - Extramural					2,949
Intramural					
Projects				0	0
Training				0*	0
Subtotal - Intramural					0
TOTAL NUTRITION RESEARCH AND TRAINING					$ 2,949

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-6

National Institute of Allergy and Infectious Diseases
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	18	1,393		
	Clinical trials	0	0		
	Total			18	1,393
Program projects:	Regular	1	110		
	Clinical trials	0	0		
	Total			1	110
Contracts:	Regular	1	43		
	Clinical trials	0	0		
	Total			1	43
Centers:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Research Resources Support				0	0
Reimbursement agreements				1	10
Career Development Awards				1*	25
New Investigator Research Awards				0*	0
Training:	Training grants	0*	0		
	Fellowships	0*	0		
	Total			0*	0
Subtotal - Extramural					1,581
Intramural					
Projects				1	98
Training				0*	0
Subtotal - Intramural					98
TOTAL NUTRITION RESEARCH AND TRAINING					$ 1,679

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-7

National Institute of General Medical Sciences
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	15	1,064		
	Clinical trials	0	0		
	Total			15	1,064
Program projects:	Regular	1	0		
	Clinical trials	0	0		
	Total			1	0
Contracts:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Centers:	Regular	3	841		
	Clinical trials	0	0		
	Total			3	841
Research Resources Support				0	0
Reimbursement agreements				0	0
Career Development Awards				1*	39
New Investigator Research Awards				2*	74
Training:	Training grants	14*	274		
	Fellowships	1*	15		
	Total			15*	289
Subtotal - Extramural					2,307
Intramural					
Projects				0	0
Training				0*	0
Subtotal - Intramural					0
TOTAL NUTRITION RESEARCH AND TRAINING					$ 2,307

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-8

National Institute of Child Health and Human Development
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	208	11,929		
	Clinical trials	16	1,480		
	Total			224	13,409
Program projects:	Regular	11	2,464		
	Clinical trials	5	1,569		
	Total			16	4,033
Contracts:	Regular	34	2,274		
	Clinical trials	2	455		
	Total			36	2,729
Centers:	Regular	13	1,235		
	Clinical trials	1	116		
	Total			14	1,351
Research Resources Support				3	13
Reimbursement agreements				3	251
Career Development Awards				14*	438
New Investigator Research Awards				23*	505
Training:	Training grants	19*	218		
	Fellowships	14*	105		
	Total			33*	323
Subtotal - Extramural					23,052
Intramural					
Projects				28	2,963
Training				28*	820
Subtotal - Intramural					3,783
TOTAL NUTRITION RESEARCH AND TRAINING					$ 26,835

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-9

National Eye Institute
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	59	4,560		
	Clinical trials	0	0		
	Total			59	4,560
Program projects:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Contracts:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Centers:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Research Resources Support				0	0
Reimbursement agreements				0	0
Career Development Awards				1*	3
New Investigator Research Awards				4*	160
Training:	Training grants	0*	0		
	Fellowships	4*	46		
	Total			4*	46
Subtotal - Extramural					4,769
Intramural					
Projects				5	750
Training				0*	0
Subtotal - Intramural					750
TOTAL NUTRITION RESEARCH AND TRAINING					$ 5,519

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-10

National Institute of Environmental Health Sciences
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	10	1,224		
	Clinical trials	0	0		
	Total			10	1,224
Program projects:	Regular	1	636		
	Clinical trials	0	0		
	Total			1	636
Contracts:	Regular	17	2,391		
	Clinical trials	0	0		
	Total			17	2,391
Centers:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Research Resources Support				0	0
Reimbursement agreements				2	810
Career Development Awards				0*	0
New Investigator Research Awards				0*	0
Training:	Training grants	0*	0		
	Fellowships	0*	0		
	Total			0*	0
Subtotal - Extramural					5,061
Intramural					
Projects				1	305
Training				0*	0
Subtotal - Intramural					305
TOTAL NUTRITION RESEARCH AND TRAINING					$ 5,366

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-11

National Institute on Aging
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	54	2,511		
	Clinical trials	0	0		
	Total			54	2,510
Program projects:	Regular	8	1,435		
	Clinical trials	0	0		
	Total			8	1,435
Contracts:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Centers:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Research Resources Support				0	0
Reimbursement agreements				1	92
Career Development Awards				11*	80
New Investigator Research Awards				3*	68
Training:	Training grants	1*	6		
	Fellowships	1*	0		
	Total			2*	6
Subtotal - Extramural					4,191
Intramural					
Projects				4	417
Training				0*	0
Subtotal - Intramural					417
TOTAL NUTRITION RESEARCH AND TRAINING					$ 4,608

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-12

Division of Research Resources
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	1	2		
	Clinical trials	0	0		
	Total			1	2
Program projects:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Contracts:	Regular	1	11		
	Clinical trials	0	0		
	Total			1	11
Centers:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Research Resources Support				280	19,387
Reimbursement agreements				0	0
Career Development Awards				0*	0
New Investigator Research Awards				0*	0
Training:	Training grants	0*	0		
	Fellowships	0*	0		
	Total			0*	0
Subtotal - Extramural					19,400
Intramural					
Projects				0	0
Training				0*	0
Subtotal - Intramural					0
TOTAL NUTRITION RESEARCH AND TRAINING					$ 19,400

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-13

Fogarty International Center
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1985,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item	Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural				
Research grants: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Program projects: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Contracts: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Centers: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Research Resources Support			0	0
Reimbursement agreements			0	0
Career Development Awards			0*	0
New Investigator Research Awards			0*	0
Training: Training grants	0*	0		
Fellowships	4*	19		
Total			4*	19
Subtotal - Extramural				19
Intramural				
Projects			0	0
Training			0*	0
Subtotal - Intramural				0
TOTAL NUTRITION RESEARCH AND TRAINING				$ 19

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

APPENDIX C

DESCRIPTION OF RFAs, RFPs AND PAs IN NUTRITION RESEARCH

The RFP, "Community and Cohort Surveillance Program (CCSP): Central Lipid Laboratory," issued by NHLBI, sought proposals to establish a central lipid laboratory, to be used for analysis of blood samples from representative cohorts of adult men and women in four communities taking part in the CCSP. The primary objective of the CCSP is to measure associations of established and suspected coronary heart disease (CHD) risk factors (including lipids, lipoprotein cholesterol and apolipoproteins) with atherosclerosis (diagnosed by ultrasound) and new CHD events in four diverse communities, and to compare the communities with respect to risk factors, medical care, atherosclerosis and CHD incidence. The project includes four field centers, a coordinating center, a central hemostasis laboratory, and a central lipid laboratory. The functions of the central lipid laboratory are to analyze blood samples for a set of lipid factors, and to take a lead role in all activities related to lipid measurements--protocol development, training quality control, and analysis and publication of results.

The RFA, "Research in Nutrition and Cardiovascular Disease," issued by NHLBI, sought applications for research projects in nutrition and cardiovascular disease (CVD), including basic, clinical, behavioral, and demonstration and education research. Experts in several disciplines, or in several areas of one discipline (such as cardiology, physiology, biochemistry, epidemiology, pediatrics, nutrition, behavioral sciences, and public health, with particular expertise in hyperlipidemia, hypertension and obesity), are encouraged to participate in research related to the role of nutrition in cardiovascular disease. Examples of projects that offer opportunity for collaborative research are: basic studies and clinical investigations to study the effects of diets or nutrients on CVD or its precursors; research on the biobehavioral factors that influence food choice and intake as they relate to CVD, as well as on the ways to improve food selection, maintenance of energy balance, etc.; metabolic ward research with direct relevance to CVD; and support of resource units to serve some of the basic, clinical and ambulatory care research projects.

The RFA, "Childhood Nutrition, Physical Activity and CV Health," issued by NHLBI, solicited applications for studies to identify and track the acquisition of food intake and physical activity patterns related to cardiovascular health. Children three or four years of age at entry into the study, from families with a high risk of coronary heart disease or stroke, will be compared with children from families with a low risk for these diseases. High risk might include coronary and stroke events in grandparents or parents, and/or coronary risk factors in parents such as obesity, hyperlipidemia, diabetes, high blood pressure, and smoking. Investigators are encouraged to study the interaction of CVD risk factors. For example, studies should address the identification of psychosocial and environmental variables associated with (and possibly predictive of) acquisition of food intake behaviors and/or physical activity behaviors that affect cardiovascular risk factors for specified age groups. Measures of

height, weight, heart rate, skinfold, blood pressure, and history and duration of breast feeding should be taken for every child and parent (except for breast feeding), along with their nutrient intake and food patterns in order to assess total caloric intake and nutrients such as fat and sodium. Assessment of usual physical activity, including leisure and work activities, is also encouraged.

The RFA, "Specialized Centers of Research in Arteriosclerosis (SCOR-A): National Research and Demonstration Centers In Arteriosclerosis," issued by NHLBI, sought applications for Specialized Centers of Research in Arteriosclerosis in order to elucidate the fundamental mechanisms involved in arteriosclerosis. The National Research and Demonstration Centers (NRDC) program is envisioned as an enhancement of the Institute's H-SCOR program through the addition of a thematically related component in demonstration and education research. The NRDCs must include the following essential elements: a SCOR-A, encompassing both basic (laboratory-based) research and clinical investigation; demonstration and education research; and an organizational unit for coordination, integration and evaluation of the entire spectrum of the aforementioned essential elements. Studies are sought to examine the etiology and pathogenesis of atherosclerosis at the basic and clinical levels; e.g., clinical and animal studies of nutrition as it relates to atherogenesis. The demonstration and education research component of the NRDC involves testing of the effectiveness of interventions to promote health or prevent disease in defined populations.

The RFA, "Specialized Centers of Research (SCOR) Concerned With Respiratory Disorders of Neonates and Children," issued by NHLBI, sought applications for clinical and basic research relative to the prevention, diagnosis and treatment of respiratory diseases of neonates and children. This research emphasizes the exploration of basic mechanisms, the elaboration of new and significant hypotheses, and the generation of novel strategies for approaching current clinical and fundamental issues related to respiratory disorders. Premature birth and very low birth weight continue to be risk factors for a number of respiratory problems that are associated with signficant morbidity during infancy and childhood. Research on neonatal respiratory distress syndrome and the role of the surfactant system continues to be of interest. However, research on other respiratory problems, such as bronchopulmonary dysplasia and apnea of prematurity, is encouraged. Since the lack of animal models hampers attempts to determine the cellular and molecular mechanisms of many of the respiratory diseases of childhood, especially bronchiolitis and cystic fibrosis, new approaches for developing model systems are also encouraged. Improved nutritional and pulmonary management has significantly improved the life span of children with cystic fibrosis; however, the nature of the primary defect in this genetic disease, and the relation of that defect to pulmonary deterioration, are still unknown.

The RFA, "Workplace Demonstration and Education Research in Cardiovascular Diseases," issued by NHLBI, sought applications for studies to test whether effective methods of risk factor reduction used in

other settings can be adapted successfully to the workplace, specifically for cardiovascular health promotion/disease prevention (HP/DP) programs. Since effective major risk factor interventions have been developed and validated in a variety of HP/DP programs for cardiovascular disease, the primary aim of this RFA is to invite applications to pursue the following objectives: 1) to determine how these successful methods for major CVD risk factor interventions can be adapted for use in the workplace, and to test whether they are clinically and behaviorally effective in the workplace; 2) to compare and evaluate in the workplace strategies to modify two or more risk factors with strategies to modify a simple major CVD risk factor; and 3) to test selected health education approaches to enhance compliance with interventions on one or more CVD risk factors. Investigations are encouraged to determine the appropriate methods for achieving and maintaining long-term dietary changes in this setting, and for evaluating changes in institutional methods of preparing foods or in the patterns of nutrient intake, particularly those known to impact blood lipid levels, blood pressure, and body weight. Nutrition knowledge related to CVD risk factors should also be assessed, and the selection of dietary adherence measures should take into consideration ease of administration, cost, reliability, and validity.

The RFA, "Cell Biology of the Vasculature in the Pathogenesis of Hypertension," issued by NHLBI, sought applications for the support of cellular biology research approaches to the role of vascular smooth muscle and endothelium in the pathogenesis of hypertension. Research on electrolyte transport and vascular reactivity has identified several key factors. These include ions (sodium, potassium, calcium and magnesium), and enzymes such as calmodulin, the calcium binding protein. Of the numerous factors that affect vascular smooth muscl and blood vessel contraction, the electrolyte environment of the vascular smooth muscle cells is critical. This electrolyte environment is known to differ among essential hypertensives. For example, differential sodium sensitivity exists within populations of essential hypertensives, and black hypertensives exhibit potassium excretion patterns different from white hypertensives. This interdisciplinary research including the expertise of cell biologists and hypertension researchers will enhance the understanding of the role of vascular smooth muscle, and the influence of electrolytes on the regulation of blood pressure and the pathogenesis of hypertension.

The RFA, "Exercise, Stress and Atherosclerosis," issued by NHLBI, sought applications to support research investigating the role of physical exercise as a potential mediator of the effects of stress on the development and progression of atherosclerosis. Preliminary evidence on the moderating effects of exercise on cardiovascular and neuroendocrine responsivity to environmental demand has suggested potential common pathways for mechanisms of action. Elucidation of this relationship will require the development of appropriate animal models to adequately control for genetic, dietary, developmental and environmental variables. The interdisciplinary nature of this research will require the combined expertise of biobehavioral research disciplines (e.g., psychophysiology, psychobiology, experimental psychology) in cooperation with biomedical disciplines (e.g. physiology, cardiology, neurobiology, genetics, and nutrition).

The RFA, "Cooperative Agreement: Cooperative Group for Studies on Mutagens in Human Foods," issued by NCI, solicited applications for cooperative agreements for the support of a Cooperative Group to investigate the possible role, fate, and cancer relevance of known dietary mutagens commonly present in human foods. Interest in the possible causatory or inhibitory roles of diet in human cancer has led to concern regarding the widespread occurrence of dietary mutagens in foods in terms of their genotoxic effects leading possibly to cancer induction. In order to conduct a comprehensive research program, a Cooperative Group to investigate dietary mutagens could be composed of scientists from academic, nonprofit, research and industrial organizations.

The RFP, "Preclinical Toxicology of Chemopreventive Agents," issued by NCI, sought proposals to establish master agreements to evaluate the acute, subacute/subchronic and chronic toxicity of designated chemopreventive agents. Studies will be performed in animals (rodents and dogs) and will include conventional short-term studies, lifetime studies, and multigeneration teratogenicity studies. The chemopreventive agent will be given primarily by the oral route. The following four tasks are required: 1) perform acute toxicity, pilot-dose-range finding and 13-week subchronic toxicity studies; 2) develop a protocol for a pharmacokinetic profile for each agent; 3) develop and perform teratogenicity studies on chemopreventive agents that have the prospect of being administered to women of childbearing potential; and 4) perform chronic 1-year oral toxicity studies. Potential chemopreventive agents include several naturally occurring substances, such as vitamin A and its precursor beta-carotene, ascorbic acid, alpha-tocopherol, and selenium, as well as antioxidants, phenols, indoles and prostaglandin synthesis inhibitors. Retinoids have been actively investigated for their anticarcinogenic potential. Human trials in cancer prevention are under way with two such retinoids, the all-*trans* and 13-*cis* isomers of retinoic acid.

The RFA, "Cancer Control Small Grants Research Program," issued by NCI, sought applications to encourage scientists from a variety of academic disciplines to investigate the following areas: human intervention research in cancer prevention (chemoprevention, diet and nutrition, occupation and early detection); community oncology (improving application of patient management and continuing care research advances in community settings); and health promotion sciences (modifying personal, social and life-style and health care system factors that contribute to cancer prevention and control). Cancer control is defined as the reduction of cancer incidence, morbidity, and mortality through an orderly sequence from research on interventions and their impact in defined populations to the broad, systematic application of the research results.

The RFA, "The Physiology of Lactation and the Biology of Human Milk," issued by NICHD, solicited applications for studies to explore the physiological processes occurring in the breast from the time of conception through lactation and weaning in order to understand the development and function of lactating tissue. Also, the functional

properties of colostrum and human milk need to be evaluated in terms of their role in infant development. The influence of the entire maternal situation (such as nutritional status, environment, stress, life-style and health) on the functional properties of milk also needs to be addressed. Studies are proposed to examine the role of maternal nutrition and metabolism on the development and maintenance of lactation; the metabolic and functional changes in the breast that lead to lactation; the organization and function of the lipid fraction of human milk (e.g., the effects of maternal diet and habit on lipid composition as well as on the packaging of lipid and other compounds sequestered in the lipid fraction); the functional properties associated with subcellular organized particles; and the function and organization of immune components in milk and their relationship to the establishment of the intestinal immune system of the infant.

The RFP, "Longitudinal Studies on Development of Obesity in Young Black and White Females--Clinical Centers," issued by NHLBI, sought proposals to establish collaborating clinic sites to conduct long-term prospective studies involving both black and white females, nine and ten years of age at entry. Investigators will study the incidence of obesity, the predictors of transition to the obese state, and the correlates of this transition, with emphasis on the relationship of this transition to other cardiovascular disease risk factors. Clinic sites must identify and enroll 500-700 participating females plus parents in 1 year, with an equal number of blacks and whites. The population may be from rural or urban areas and from a wide range of socioeconomic levels. Investigators will require expertise in performing an abbreviated physical examination and obtaining anthropometric measurements; dietary information (food pattern and nutrient intake); measures of habitual and leisure time physical activity; lipid, lipoprotein and apolipoprotein profiles; information on family socioeconomic status; and the psychological and sociological information related to obesity.

The RFP, "Factors Associated with Premature Births Derived from Vital Statistics and Hospital Records Abstraction," issued by NICHD, sought proposals from organizations capable of obtaining accurate information on the very low birth weight infant (<1,500 grams). Based on the number of infants weighing <1,500 grams from the participating states, control infants will be selected from the 1,500- to 2,499-gram and the $\geq$2,500-gram birth weight groups of infants. Control infants will be matched to the very low birth weight infants, using such variables as ethnicity, maternal age, and parity outcome of delivery. To further delineate the problems of the very low birth weight infant, mortality will be ascertained throughout the first year of life for the birth cohorts within each geographic area. The information to be obtained from the hospital or physician records include indices of fetal maturity such as birth weight, gestational age, length, and head circumference; race and ethnic origin; maternal prepregnant weight and height; and maternal weight gain during pregnancy.

The RFP, "Honolulu Heart Program," issued by NHLBI, is intended to extend the ongoing epidemiology and pathology studies of a cohort of 8,000 men of Japanese ancestry living in Hawaii. The study objectives include: continuing surveillance for new cases of coronary heart disease (CHD), stroke, other cardiovascular disease and total mortality; continuing analysis of risk factors associated with all forms of cardiovascular disease, and the prognosis after onset of specific clinical subgroups of disease; re-examination of a subgroup of the cohort for changes in and determinants of serum lipoprotein levels; and continuing analysis of risk factors associated with anatomic pathology of the heart and blood vessels, including special emphasis upon dietary intake and psychosocial processes. The Honolulu Heart program, one of the largest cohort studies in the world, was initiated to verify the reports that men of Japanese ancestry living in the U.S. had a much higher risk of CHD and a lower risk of stroke than Japanese men in Japan. The program provides the opportunity to compare disease frequencies, pathologic findings, and disease predictors with those observed in other national and international cohorts supported by NHLBI.

The RFP, "Development of Methods of Analysis of Human Colostrum and Milk," issued by NICHD, sought proposals to develop new highly accurate, quick and cost-effective methods for the analysis of specific components of human colostrum and milk. More advanced methodology is needed in the following areas: the separation of milk lipids, protein, nonprotein nitrogen and carbohydrates into their component classes; development of techniques for processing human milk and colostrum that destroy bacterial and viral contaminants without destroying biologically useful properties; analysis of the differential concentrations of components within various fractions of milk and colostrum; the analysis of vitamins and their vitamers as well as the nonprotein nitrogen of human milk; techniques to determine the structure and organization analysis of milk lipids and fatty acids; techniques for the preparation of milk samples that allow for both quantitative and qualitative analysis of drugs and environmental contaminants; and the analysis of the mineral and enzyme content of colostrum and human milk.

The RFP, "Animal Models for Studies of Neural Tube Defects," issued by NICHD, sought proposals for the development of animal models and studies of mechanisms resulting in neural tube defects. Neural tube defects include spina bifida, anencephaly and congenital hydrocephalus. At least three types of procedures may be used to produce neural tube defects in animal models: surgical, teratogenic, and genetic. Maternal deficiencies of riboflavin and zinc are involved in some neural tube defects. Some studies also suggest that neural tube defects in humans may be prevented by periconceptional vitamin supplementation; folic acid is one of the most important dietary supplements. A concerted effort is needed toward understanding the underlying developmental biological mechanisms of neural tube defects. For example, cellular and molecular studies are needed in order to consider such factors as genetic mechanisms, cell proliferation, cell migration, cellular recognition and interaction, cell differentiation, cellular protein changes, tissue interactions be-

tween neuroepithelium, etc. Consideration could also be given to studies of agents that can alter or counteract the teratogenic effect of a known teratogen.

The PA, "Studies on Exercise Physiology and Aging," issued by NIA, solicited applications for research in exercise physiology and exercise medicine related to the aging processes, and age-related diseases and disorders. Of essential concern is the question, to what extent and under which conditions is the recommendation of physical activity medically reasonable for either healthy or disease-afflicted elderly? Basic or clinical research, involving not only healthy human subjects but also suitable animal models, is needed to answer this question. Studies are needed to elucidate the influence of aging on the mechanisms for biological adaptation to exercise, from system/organ level to cell/molecular level; to define the relationship between exercise and nutrition in providing independent and healthy years for the elderly; to examine the mechanisms through which physical activity regulates behavior and psychosocial function in the elderly; to assess the role of acute and chronic exercise in the regulation of immunologic events involved in resistance to and recovery from infectious diseases in the elderly; and to define quantitatively the criteria by which the prescription of exercise is safely formulated to fulfill individual needs of healthy elderly and of people in older age categories affected by various kinds of diseases.

The RFP, "Twin Study Third Examination," issued by NHLBI, sought proposals for a third clinical examination of twins who are participants in the NHLBI Twin Study. The examination will emphasize cardiovascular and pulmonary disease risk factors and endpoints, and the assessment of subclinical disease through noninvasive techniques. Four field centers located at or near Indianapolis, Indiana; and Davis, San Francisco, and Los Angeles, California, are to perform the clinical exam of survivors of a cohort of veteran twins drawn from the National Academy of Sciences/National Research Council Twin Registry. Examination one (1969-1973) consisted of data on personal and family history, medical and dietary history, and physical examination, as well as tests of blood lipids (HDL cholesterol, total cholesterol, and triglycerides), etc. Examination two (1981-1982) included similar tests, as well as additional tests on pulmonary function and collection of environmental data. The objectives of the third examination are: to assess the incidence of cardiovascular and pulmonary diseases through a standard physical examination and medical history, and to test the hypothesis that heritability of cardiovascular diseases exceeds expected levels, which are based on known genetic risk factors; to measure the levels of known and potential risk factors for cardiovascular disease for analysis relative to the earlier measurements and to the occurrence of disease; to assess the prevalence for all twins, and incidence for a subgroup of twins, of preclinical cardiovascular disease through a graded exercise test.

The RFA, "Cooperative Multicenter Network of Neonatal Intensive Care Units," issued by NICHD, sought applications for a multicenter cooperative clinical study designed to investigate the safety and effica-

cy of new treatment and management strategies for infants in Neonatal Intensive Care Units (NICUs). Evaluation of these strategies will be facilitated by establishing a network of centers that, by vigorous patient evaluation using common protocols, can study large numbers of patients and provide answers more rapidly than individual centers acting alone. Examples of diagnostic and therapeutic questions to be answered include the nutritional and immunological advantages and/or disadvantages of using premature human milk; the use of hyperalimentation and the determination of quantity and quality of nutrients for optimal growth and development of very low birth weight infants; the use of vitamin E; and research on techniques of nursing care in the management of premature infants.

The RFP, "Development of Obesity in Young Black and White Females--Coordinating Center," issued by NHLBI, sought proposals to establish a coordinating center to collect, process and analyze data, design study forms, and perform other functions for the collaborating clinic sites that will conduct long-term prospective studies of the development of obesity in both black and white females. This study, as described earlier, will attempt to determine the incidence of obesity, predictors of transition to the obese state, and the correlates of this transition, with emphasis on the relationship of this transition to other cardiovascular risk factors. For the Coordinating Center, the three phases of the study are as follows: in phase I, measurement techniques, protocol and data collection forms for the examinations shall be standardized; in phase II, the data from the clinic sites shall be collected and processed for initial baseline screening and thereafter for four annual examinations; in phase III, the data collection, data analyses, and preparation of reports shall be completed. Data to be collected include body measurements such as height, weight, skinfolds, food pattern and nutrient intake, serum total proteins, albumin, serum calcium, phosphorus, magnesium, habitual physical activity and/or fitness test, health and nutrition knowledge and attitudes, etc.

The RFP, "Case Control Study of Cancer and Drinking Water Contaminants," issued by NCI, sought proposals for a population-based case control study, using mailed questionnaires, on the incidence of cancers of the colon, rectum, bladder, brain, pancreas, liver and kidney within a defined geographic area. Cases will total approximately 2,500, with 300-600 for each type of cancer. Fifteen hundred control subjects will be randomly selected from the general population, frequency-matched to the expected overall proportion of cases in strata specific for sex and age. The questionnaires will include basic demographic data, a lifetime residential history, and a brief dietary section, as well as data on smoking, occupation, and primary source of drinking water. The primary focus is the evaluation of hypotheses concerning the relationship of chlorination byproducts and other contaminants in drinking water to the risk of the aforementioned cancers. An adjunct environmental survey of drinking water quality will include the collection and analysis of samples of treated drinking water from community water supplies for levels of trihalomethanes, other selected volatile organics, nitrates, pesticide residues and other possible contaminants.

The RFP, "Synopsis to Review the Literature for Data Relevant to Carcinogenesis," issued by NCI, sought proposals for a master agreement to accomplish the following three objectives: 1) to review the literature for data relevant to the area of carcinogenesis and toxicology with respect to the presence of carcinogens in various environmental media, including air, water, food, drugs, cosmetics and the workplace; 2) to perform a range of tasks, including supplying bibliographies covering specific topics of interest, and providing critical analyses in defined areas of carcinogenesis and toxicology; and 3) to prepare special reports in specific formats, organize and enter data for computer-based files, and perform other tasks such as updating, modifying or editing previously prepared reports for the Division of Cancer Etiology.

The RFA, "NonInvasive Assessment of the Normality of Single Pregastrula Embryos," issued by NICHD, sought applications to encourage research and development of rapid, noninvasive measurements of single eggs or embryos; these measurements can be used to determine the probability that an individual egg or embryo will undergo normal development, safe transfer and successful implantation, or to provide early indications of problems in development. Studies should compare embryos raised in vivo and in vitro, and evaluate successful embryo transfer and subsequent development. The uptake of natural compounds by the egg or embryo from the culture medium could be determined by measuring the depletion of compounds from the medium, i.e., pyruvate, glucose, other energy sources, amino acids, nucleosides, fatty acids, ions, proteins, gases, etc. Also, compounds released from the egg or embryo into culture medium could be measured. Such compounds might include hormones, neurotransmitters, other low molecular weight compounds, ions, gases, and secretory proteins, as well as other proteins or molecules of the cell surface that can be identified by transient, noninvasive assays.

The RFP, "Support Service for the Diet, Nutrition and Cancer Program," issued by NCI, sought proposals to provide support for the Diet, Nutrition And Cancer Program. Task I includes: general support involving data and computer assistance, e.g., the development and maintenance of the nutrient analysis system for use in research and in manuscript development; the development of techniques to assist in solving problems related to retrospective nutrient data collection, educational methodology, and research evaluation, e.g., design, development and testing of diet and nutrition data collection forms and techniques; provision of assistance for the planning and formation of technical documents, including the preparation and review of technical papers, publications resulting from workshops and conferences, and the annual nutrition research budget report for the NCC; and provision of workshop, conference and meeting support. Task II involves providing the analytical, data management, computer programming and coordination support for intervention clinical trials related to diet, nutrition and cancer.

The RFP, "Effect of Toothbrushing with 0.4% Stannous Fluoride Gel on Periodontal Health," issued by NIDR, sought proposals for the conduct

of an 18-month longitudinal clinical trial to study the clinical effect of toothbrushing with an American Dental Association-accepted fluoride dentifrice in combination with additional toothbrush application of a 0.4 percent SnF_2 gel, a 0.22 percent NaF gel, or a fluoride-free gel. The effects of the three treatments will be studied in three groups of approximately 125 persons, ages 18-28 years, who demonstrate generalized existing gingivitis and bleeding upon probing and who would be classified as periodontal case Type I. Variables to be measured will be the presence of gingivitis, gingival bleeding upon probing, periodontal probing depth, probing attachment level, supragingival dental plaque, and the presence of extrinsic dental stain.

The RFP, "Investigations of Tumors that Occur Excessively Among Blacks," issued by NCI, sought proposals for a multicenter population-based case control investigation of four specific types of cancer--multiple myeloma and cancers of the esophagus, pancreas and prostate--that yield excess rates in blacks. Personal interviews conducted with individuals who develop one of the four cancers and with population-based control subjects will focus on identifying the race-specific risk factors for these tumors, and determining the extent to which these risk factors might explain the differences between blacks and whites. Approximately four Collaborating Centers will undertake both research and support activities, while one Coordinating Center will be involved only in support activities. The interviews will be conducted in the home, with 3,200 cases equally split between blacks and whites and 2,400 control subjects; four separate questionnaires containing sections on tobacco and alcohol consumption, occupation, demographic factors including social class, access to medical care, biomedical conditions and a limited dietary interview will be administered. Depending on the type of cancer, an extended dietary history, sexual history, and history of exposure to ionizing radiation, along with an assessment of prior antigenic stimulation, will also be administered.

The RFP, "Ethnic Differences in Life Style, Psychological Factors and Medical Care During Pregnancy," issued by NICHD, sought proposals for a study to obtain a quantifiable description of behavior and lifestyle differences among women of different ethnic groups that are known to differ in their rates of low birth weight. Phase I includes the design of forms for collecting information on psychological stress, social support, diet (including 24-hour recall), physical activity and fatigue, and attitudes, beliefs and practices with regard to pregnancy in general. A demographic questionnaire and a medical record abstraction form will be developed to collect data on each subject's age, gravidity, parity, race or ethnic group, marital status, reproductive history, height, weight, alcohol use, etc. Phase II includes the recruitment and interview of approximately 600 pregnant women over 18 years of age from at least three of the following ethnic groups: Mexican, Chinese, American Black, Puerto Rican, and White. Phase III includes the analysis, interpretation and reporting of the data.

The RFA, "Differentiating Agents in Human Malignancies," issued by NCI, solicited applications for basic research studies of in vitro and in vivo systems for measuring differentiation and maturation effects of different agents in human tumors, and for concurrent clinical trials to establish the validity of these measures in the clinical setting. The current concept that cancers are composed of cells blocked at an early stage of normal maturation has stimulated a search for agents with potential differentiating effects. Retinoids were the first compounds shown to induce differentiation in a number of in vitro systems. Subsequently, polar solvents, fatty acids, vitamin D analogues, and several cytotoxic agents (pyrimidines, purines and anthracyclines) have been shown to cause differentiation in vitro at doses below the cytotoxic levels. Research is needed in order to develop accurate and precise measurements of the treatment effect of the potential differentiating agents at the clinical level.

The RFP, "The Framingham Study Physical Examination, Testing and Surveillance," issued by NHLBI, sought proposals for a prospective study related to the treatment, diagnosis, and prevention of cardiovascular disorders, using the Framingham Heart Study (FHS) cohort. The following research questions will be addressed: how does the incidence of coronary vascular disease in the offspring, controlling for the major CVD risk factors, relate to the clinically documented occurrence of CVD (morbidity and mortality) in parents (FHS cohort subjects); does information obtained from noninvasive tests contribute to the prediction of overt cardiovascular disease in a sample initially free of CVD; to what extent do lipoprotein cholesterol levels relate to the incidence of clinically recognizable CVD in a population of young adults followed for up to 18 years; and what have been the secular trends of risk factors for cardiovascular disease in these subjects compared with those for their parents at similar ages.

The RFA, "Cooperative Agreement on Cooperative Multicenter Program on Environmental Conditions for Nonhuman In Vitro Fertilization and Preimplantation Development," issued by NICHD, sought applications for basic and applied research dealing with in vitro fertilization, preimplantation development and embryo transfer techniques in nonhumans. Basic research activity using in vitro fertilization, in vitro preimplantation embryo development and embryo transfer is increasing rapidly. The culture conditions in use bear little resemblance to the in vivo conditions; current understanding of nutritional requirements and basic principles of nutrition is practically nonexistent; and embryos raised under these conditions are inferior. Research is needed to provide a new comprehensive understanding of the general principles of nutrition, particularly with regard to the interaction of the preimplantation embryo with the maternal environment. An important impetus underlying this research initiative is the increasing use of in vitro fertilization, preimplantation development and implantation as model systems for reproductive toxicology studies. Studies are needed on the different aspects of the culture environment, i.e., micronutrients, macronutrients, and other aspects of the environment.

The RFA, "Cooperative Agreements for National Collaborative Chemoprevention Projects," issued by NCI, sought applications for projects to investigate new approaches to cancer prevention in order to: acquire basic knowledge of significant biological systems for carcinogenesis/anticarcinogenesis; derive new insights into practical means for chemoprevention of the carcinogenic process; and rapidly translate this information into new chemopreventive entities with known ranges of efficacy and defined pharmacological/toxicologic properties. The classes of chemopreventive agents that appear promising include protease inhibitors, antioxidants, dithiolthiones, dehydroepiandrosterone and related analogs, cyanates and isothiocyanates, inhibitors of arachidonic acid metabolism, nucleophiles, and potential new classes of inhibitors existing in natural products such as the yellow and green vegetables.

The RFA, "Neurologic, Muscular, Perceptual and Cardiovascular Aspects of Falls and Gait Disorders in Elderly Persons," issued by NIA, sought applications for investigations to determine the neurologic, muscular, perceptual and cardiovascular factors responsible for the various types of falls and disabling gait disorders in elderly people, and to elucidate the underlying pathophysiological mechanisms. Areas of interest include: the effects of neurologic and other chronic diseases of the elderly, and of medications widely used by the elderly, on gait and balance control mechanisms; the effect of habitual physical activity or specific nutrients on the neuromuscular control of postural stability and gait; the contribution of abnormalities in vestibular function, proprioception, or visual/spatial perception to the risk of falling; etc. Epidemiological, clinical, experimental and pathological investigations, as well as studies of valid animal models, are encouraged.

The RFA, "Studies on Novel Human Exogenous and Endogenous Retroviruses," issued by NCI, sought applications for studies to characterize the multiple uncharacterized type-C virus particles and endogenous human retroviruses and determine their significance in human cancer. Basic studies are needed to identify and characterize protein and nucleic acid components of uncharacterized type-C virions by modern technology, as well as on viral origin, distribution and expression in different types of human and non-human tissues. One particular area of interest is to develop tissue culture methodologies suitable for cultivation of difficult-to-grow human tumor cells that may have an infectious etiology, such as Hodgkin's disease, breast cancer, and B cell lymphomas, using growth factors, special nutrients, and newer specialized cell growth technologies.

APPENDIX D

FY 1985 SCIENTIFIC SEMINARS

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In FY 1985, nine scientific seminars in nutrition were presented at the monthly NCC meetings. These presentations were by scientists engaged in nutrition research who are supported by the extramural and intramural programs of NIH. Descriptions of the seminars follow.

1) "Interaction of Nutrition and Infection in the Developing World," was presented by Robert Black, M.D., associate professor of medicine and preventive medicine, University of Maryland School of Medicine, at the November 1, 1984, NCC meeting. A summary of his presentation is given below.

Diarrhea and malnutrition are common in young children in developing countries and a reciprocal relationship has been postulated with diarrhea leading to malnutrition and malnutrition predisposing the children to diarrhea. Although several studies have suggested that nutritional status is a determinant of the prevalence of diarrhea, few of these studies have considered whether an increased prevalence is due to an increased incidence of diarrheal episodes, a longer average duration of illness, or a greater propensity of malnourished children to have specific types of diarrhea (e.g., shigellosis or giardiasis) that are associated with a longer illness. Alternatively, intestinal malabsorption, frequently associated with severe malnutrition, may be responsible for noninfectious diarrhea in the more undernourished children.

In order to address these questions, longitudinal studies carried out in rural Bangladesh examined the interactions between the nutritional status of children and infectious diseases, including whether malnourished children have an increased incidence or duration of diarrhea. A village surveillance system was used to determine the incidence, prevalence and severity of malnutrition and a variety of common diseases, including diarrhea associated with specific etiologic agents. Of the common illnesses reported, only the prevalence of diarrhea had an inverse relationship with increments in weight during two-month periods and with linear growth during one year. These findings were similar to those seen in children of Guatemala, Mexico, and Gambia.

As a consequence of diarrheal illnesses, linear growth of the children was reduced 2 centimeters by 5 years of age and was 10 centimeters less than that of a child in the National Center for Health Statistics (NCHS) reference population. Thus, approximately 20 percent of the difference in linear growth could be attributed to diarrheal diseases. Children with a high prevalence of diarrhea, largely accounted for by one or more prolonged diarrhea episodes, had the greatest growth retardation. Each episode of prolonged diarrhea was associated with linear growth cessation, and little or no catch-up growth after recovery.

These data, however, do not address whether the high prevalence of acute diarrhea or chronic diarrhea per se exerts the greatest negative effect on growth. Frequent episodes of acute diarrhea may be as

detrimental to nutritional status as chronic diarrhea. Diarrhea's adverse effects on growth may be due to a reduced dietary intake due to anorexia and food withdrawal during illness, and/or nutrient malabsorption. Nutrients ingested during illness may be lost due to accelerated intestinal transit time, or to malabsorption resulting from transient decreases in digestive enzymes, damage to the mucosal surface, or bacterial overgrowth of the small intestine.

Upon investigation of diarrhea associated with specific etiologic agents, the most frequently found pathogens were enterotoxigenic Escherichia coli (ETEC) and Shigella flexneri. These pathogens accounted for 30 percent and 15 percent of the diarrheal episodes, respectively, and for more than 50 percent of the prolonged episodes of diarrhea. The duration of the ETEC diarrhea appeared to be inversely related to the child's nutritional status. Diarrhea due to ETEC had a significant negative effect on the bimonthly weight gain of children, and that due to shigellosis had the strongest negative effect on bimonthly and annual linear growth. Diarrhea due to Shigella flexneri was usually dysenteric, associated with blood and mucus in the stool, and of a longer duration than other types of diarrhea (16 percent of the episodes lasted more than 20 days). Shigellosis also resulted in a loss of serum protein, which may have been partially responsible for the linear growth failure; observations made in other populations have indicated that protein intake is an important determinant of linear growth.

Another analysis evaluated the incidence and duration of diarrhea associated with various bacterial, viral and parasitic pathogens as a function of the children's prior nutritional status. Among children in the first 2 years of life, the degree of wasting measured as the child's relative weight for length was the strongest anthropometric predictor of diarrheal duration. The mean duration of diarrhea in the lowest weight for length group was 56 percent longer than the duration for children who were at least 90 percent of the NCHS standard. The study did not demonstrate a threshold level of wasting below which there is a substantial increase in diarrheal duration. The child's nutritional status did not appear to be related to the incidence of diarrhea in general, or of ETEC or Shigella diarrhea.

The possible explanations behind the longer durations of diarrhea in malnourished children are: the duration of diarrhea may be a function of the number of bacteria that enter the small intestine (which probably does not differ according to nutritional status in the children) and certain host factors such as the rates of immune response and intestinal repair; malnourished children may have delayed recovery of the intestinal mucosa after infection from Shigella, ETEC, cholera, etc., which could result in a more prolonged diarrhea; and malnourished young children may suffer from persistent lactose malabsorption, a common reason for prolonged diarrhea after an acute enteric illness.

Dr. Black concluded that diarrhea had an adverse effect on growth; ETEC diarrhea had the most pronounced effect on short-term weight gain and Shigella diarrhea had the largest effect on annual linear

growth in children. Malnutrition did not seem to predispose to an increased incidence of all diarrhea of the two most frequent types of diarrhea affecting the study children. Malnourished children, however, did experience diarrhea of longer duration, which may explain the increased prevalence of diarrhea noted in malnourished children.

Thus, it appears from this research that controlling diarrhea, especially that due to ETEC and Shigella, would not only substantially decrease morbidity, but also improve the growth and nutritional status of these children. However, nutritional interventions alone are not likely to reduce the high incidence of diarrhea, but efforts to improve the child's nutritional status may be successful in limiting the duration of diarrhea and its negative nutritional consequences. Individualization of nutritional therapy for diarrhea in malnourished children may offer the best solution to this serious problem of young children in developing countries.

2) "Breast Feeding and Toxigenic Intestinal Infections: Missing Links in Crib Death?" was presented by Stephen S. Arnon, M.D., Infectious Disease Section, Department of Health Services, State of California, at the December 6, 1984, NCC meeting. A summary of his presentation is given below.

Crib death, or sudden infant death syndrome (SIDS), is the leading cause of postneonatal death in the developed world; more children die from SIDS during the first year of life than from any other single cause, except accidents, during their next 13 years. In the United States alone, approximately 6,000-8,000 infants die of SIDS annually, an incidence of 1 to 2 per 1,000 live births. Most investigators consider SIDS a composite of various etiologic entities that have eluded identification by presently available diagnostic techniques. However, new studies of infant botulism have prompted a new perspective on crib death.

Infant botulism is an infectious disease in which ingested spores of Clostridium botulinum germinate, multiply, and produce their own toxin in the intestinal lumen of the infant. Botulinal toxin, the most potent poison known, is then absorbed, carried and bound irreversibly to motor nerve endings, causing flaccid muscle paralysis. When the airway and respiratory muscles are sufficiently paralyzed, death results. In California, the incidence of hospitalized cases of infant botulism is 10 per 100,000 live births and the case fatality ratio is 3 percent.

The possibility that rapid onset of infant botulism might be one cause of SIDS was suggested by the potency and mechanism of action of the toxin; by the absence of histologic effects from the toxin; and by the observation that some infants subsequently hospitalized with infant botulism has simply stop breathing while in their mothers' arms. Investigation of autopsy material has disclosed evidence of C. botulinum and its toxin in specimens from infants with SIDS in California, Massachusetts, Washington, Utah and Switzerland. However, for methodological reasons, the exact proportion of SIDS

cases that might be attributable to infant botulism is not known. At present the proportion appears to be in the 5-15 percent range.

In addition to these observations, the similarity of the age distribution of infant botulism to that of patients with SIDS suggested that factors accounting for the pathophysiology of infant botulism might also be important for some SIDS cases. The influence of different milk diets is one factor under investigation, since human milk and formula milk differ in their immunological composition and in their influence on the normal intestinal microflora, against which C. botulinum must compete in order to cause illness.

Studies have shown that secretory IgA (S-IgA) antibody that can specifically agglutinate vegetative cells of C. botulinum is present in human milk. Variation in the severity of infant botulism appears to be associated with the infants' milk source; all 10 C. botulinum positive sudden death cases in California, indistinguishable from typical crib death, occurred in formula-fed infants, whereas cases with a more gradual onset of infant botulims that resulted in hospitalization occurred in predominantly breast-fed infants. In addition, S-IgA can be present both in the milk of mothers whose children have never had infant botulism, as well as in that of mothers whose babies have had infant botulism.

The biologic variability in the possible protective role of breast feeding in SIDS may be explained in part by the presence, the specificity, and the titer of the antibodies in human milk. Antibodies present in human milk directed against C. botulinum demonstrate effective functioning of the "mucosal immune system," a term used to describe the physiological process connecting a lactating woman's intestine to the protective immunological factors in her milk (which include S-IgA antibody, lactoferrin, lysozyme, complement, and leukocytes). This system involves the sensitization of lymphocytes in the lymphoid tissue of the mother's intestine to indigenous or ingested foreign antigens (e.g., foodstuffs and bacteria); these cells migrate to the breast, where they produce antigen-specific S-IgA antibody.

In contrast, the formula-fed infant is deprived of the immunological components in human milk. Therefore, the formula-fed infant may experience rapid intestinal growth of and toxin production by a variety of bacteria, and may also be deprived of adequate amounts of nutritional substances such as taurine that are essential for normal development.

In addition to the infant botulism caused by C. botulinum, other pathogenic clostridia such as C. difficile and C. perfringens may also be candidates as causes of the toxigenic intestinal infections of infancy. For example, in studies of infant monkeys injected with microgram amounts of C. difficile toxins A and B, either toxin caused a quiet death within 4-10 hours that was clinically and pathologically consistent with human SIDS. However, the evidence that C. difficile toxins cause SIDS is not conclusive; blood serum and tissues need to be examined to determine whether toxigenic bacteria,

particularly certain clostridia, colonize the infant intestine and produce their toxins, thereby causing SIDS.

Dr. Arnon concluded that it is improbable that the congruence of the age distributions of infant botulism and of SIDS is a coincidence. Continuing investigations are needed on the epidemiology and pathophysiology of infant botulism and other putative toxigenic intestinal infections of infancy in order to yield insight into these potentially preventable causes of SIDS.

3) "Gastric Cancer and Diet," was presented by Ritva Butrum, Ph.D., acting chief, Diet and Cancer Branch, Division of Cancer Prevention and Control, NCI, at the January 10, 1985, NCC meeting. A summary of her presentation is given below.

Gastric cancer incidence and mortality is relatively high in many countries of east Asia, Latin America, and eastern and northern Europe, whereas overall mortality rates from gastric cancer are very low in the United States. In the U.S. population, however, large differences in rates occur between ethnic groups and between cultural groups within the same racial group. Hispanics, blacks and native Americans (Indians) have a much higher incidence rate of gastric cancer than the general U.S. and "Anglo" populations. These statistics suggest a cultural/environmental influence on gastric cancer and thus a possible dietary role.

Human migration studies have provided the most valuable advances in gastric cancer epidemiology over the past 20 years. They have indicated that the prevalence of gastric cancer within the population is not related to genetic determinants, but rather to environmental influences during early life. For example, persons who migrate from an area of high risk for gastric cancer to one of low risk still experience the high risk characteristic of the country of origin. However, the offspring of the immigrants experience the risk characteristic of the new country. These risk characteristies have been clearly documented in the Japanese and native-born residents of Hawaii, among Icelanders and other ethnic groups who migrated to Manitoba, Canada.

Many possible associations have been proposed between dietary intake and risk of gastric cancer, since food first comes into contact with the gastrointestinal tract in the stomach and remains there for rather long periods. Although no single relationship is universal, several studies have shown that populations consuming large amounts of nitrates and nitrites and/or highly salted, smoked, and pickled fish and meat, together with small amounts of vegetables and fruits are at greater risk for developing gastric cancer. There appears to be a beneficial effect of consuming foods rich in vitamins C and A, Studies have linked salt to the etiology of gastric cancer, since most of the dietary components positively associated with gastric cancer contain added salt. One widely accepted etiologic model for gastric cancer is that a high salt intake may cause injury to the gastric mucosa, resulting in gastritis which subsequently leads to a decrease in acid output and thus a rise in the stomach pH. The

microbial flora then increases and becomes capable of nitrate reduction, which in turn leads to steady, long-term formation of carcinogenic N-nitroso compounds that may eventually cause cancer. Antioxidants such as vitamins A, C, and E and selenium can interfere with the nitrosification of amides and amines, and therefore theoretically may be able to halt this chemical process. Thus, the salt hypothesis does not exclude the possibility that intakes of vitamin C and nitrate/nitrite also may be important in the etiology of gastric cancer, but rather implies that no evidence is currently available implicating them in the etiology.

Other studies have suggested that dietary deficiencies of vitamin A, known to result in a deterioration of the stomach's protective mucus lining, might also cause the epithelial tissue in the stomach to be more susceptible to the effects of putative carcinogens in the diet. This hypothesis is consistent with observed temporal trends of disease incidence within and between countries and with other descriptive variables related to the availability, quality and consumption patterns of foods containing vitamin A. Based on this model, results have shown a consistent, albeit weak, indication of heightened risk of stomach cancer due to deficiencies of vitamin A intake. However, these results may simply be indicative of the relationship of stomach cancer incidence to other dietary components closely related to vitamin A intake.

One of the key issues in the relationship of diet to gastric cancer lies in the possible carcinogenic role of N-nitroso compounds. These compounds can be produced in the stomach as the result of a union between nitrates or nitrites in food and amides or amines derived from protein. Nitrosamines are unstable and thus may harm the mucosa; nitrosoureas and nitrosocarbamates have produced stomach cancer in rodents. A strong positive correlation between per capita daily levels of nitrate ingestion and gastric mortality has been found in 12 countries; the threefold decrease in gastric mortality in the U.S. since 1925 parallels the approximately fourfold decrease in average gastric nitrite load. Most studies attempting to correlate gastric cancer with nitrate intake have dealt primarily with nitrate in the drinking water, since exposure is similar for the entire population. The populations with a higher average intake of nitrates have been shown to be at a higher risk for stomach cancer. For example, in Japan gastric cancer was found to be more common in farmers who drank well water, often high in nitrates, than in those who drank surface water. In addition, a study of patients with atrophic gastritis indicated significantly elevated levels in the concentrations of nitrite and nitrosamines in the gastric juice of these patients when compared to that of other groups. Thus, the high incidence of gastric cancer in patients with atrophic gastritis may be due to the constant exposure of an already damaged gastric mucosa to N-nitroso compounds.

Dr. Butrum concluded that the most prominent features of the descriptive epidemiology of stomach cancer include findings of a high incidence of the disease among Eastern Europeans which diminishes somewhat in second generation immigrants, and an inverse relationship

between socioeconomic level and incidence. The role of dietary factors in stomach cancer etiology has been the focus of many investigations. Improvements in the validity and reliability of measures of dietary intake through use of physiological markers would add a great deal to the quality and accuracy of investigations.

4) "Natural Toxicity of Trace and Essential Elements: Factors Provoking the High Incidence of Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia of Guam," was presented by Ralph M. Garruto, Ph.D., senior research biologist, Laboratory of Central Nervous System Studies, NINCDS, at the February 7, 1985, NCC meeting. A summary of his presentation is given below.

Amyotrophic lateral sclerosis (ALS), known on Guam as lytico or paralytico, is a disease of the motor neurons of the brain and the spinal cord characterized by progressive muscular weakness and atrophy. In the late 1940's and early 1950's, a high incidence of ALS was observed in the Chamorro people of Guam. Subsequently, the incidence of parkinsonism-dementia (PD), known locally as bodig or rayput, and recognized as another fatal neurological disorder, also was found to occur in parallel high incidence in the same villages in the same family and occasionally in the individual. PD is characterized clinically by progressive mental deterioration and parkinsonian features, including slowness of voluntary movement, rigidity, tremor and masked facies. These initial studies led to the establishment of a field research on the island in 1956 by the National Institute of Neurological and Communicative Disorders and Stroke (then known as the National Institute of Neurological Diseases and Blindness). Two other foci of high incidence of ALS and PD in the western Pacific include isolated groups living in the Kii peninsula of Japan, and the Auyu and Jakai peoples in the southern lowlands of West New Guinea.

A long-standing hypothesis about the high incidence of ALS and PD in these three regions is that it is due to chronic environmental deficiencies of alkaline earth metals such as calcium and magnesium. This hypothesis is supported by the recent discoveries of unusually low concentrations of calcium and magnesium in garden soil and drinking water in the three high-incidence foci, and the observation that approximately 30 percent of the Chamorros with ALS and PD have biochemical evidence of disturbances in calcium and vitamin D metabolism, and that Guamanian children and adults have cortical bone loss. Chronic deficiencies of calcium and abnormalities in mineral metabolism may provoke a secondary hyperparathyroidism, resulting in increased intestinal absorption of toxic metals such as aluminum, and the subsequent mobilization of calcium and heavy metals from bone and deposition of these elements in central nervous system tissue, possibly as hydroxyapatites. Deposition of calcium, aluminum and other metals in neurons may occur in utero, or during infancy, childhood, adolescence or even at a later time, but long before the onset of clinical disease. Later intake of adequate calcium and magnesium and subsequent correction of the secondary hyperparathyroidism may fail to remove the hydroxyapatite deposits in affected neurons and is unlikely to prevent or reverse the neuronal damage which has already occured.

One study showed that the soils from southern Guam had a 10- to 100-fold lower mean calcium concentration (1,000 ppm) when compared to mean concentrations for the central and northern regions of the island; the calcium concentration in soil was the lowest in Umatac village, which experienced the highest incidence of ALS and PD. Low levels of calcium were also found in soil samples from the Kii peninsula of Japan and from West New Guinea. The concentration of calcium in the drinking water on Guam was geographically parallel to calcium levels in soil; the mean calcium concentration in drinking water from southern Guam was approximately three times less than that from central and northern Guam.

In an attempt to identify both the deposition and distribution of elements in central nervous system tissue a new imaging method using wavelength-dispersive spectrometry (WDS) and computer-controlled electron beam x-ray microanalysis was used. Earlier studies using energy-dispersive spectrometry (EDS) showed intraneuronal accumulation of both aluminum and calcium in neurofibullary tangle (NFT)-bearing hippocampal neurons in ALS and PD patients but these studies were unable to determine the distribution of element within single nerurons or a field of neurons. Currently, EDS is being used to survey a tissue section prior to elemental imaging; i.e., once a positive probe site in a neuron is located, WDS is used to image the distribution of elements in a field of surrounding neurons. The computer drives a focused electron beam over a two-dimensional array on the specimen surface, and characteristic and continuum (background) x-rays and backscattered electron signals at each point in the array are collected for the various elements of interest. The resulting five dimensional array is then stored in computer memory. This method allows for a qualitative and semiquantitative determination of both the intracellular and extracellular distribution of elements within the central nervous system.

The above method has been used to clearly demonstrate the prominent accumulation of calcium, aluminum, and silicon in NFT-bearing neurons in the brain and spinal cord of ALS and PD patients. These elements are cell-specific and varying together. The elemental images clearly show the striking colocalization of these elements within the cell body and dendritic processes of the same NFT-bearing neuron. The concentration and distribution of these analytes varied from neuron to neuron. The semiquantitative estimates of the calcium, aluminum, and silicon concentrations (weight fraction) in the NFT-bearing neurons from ALS and PD patients were 7,200, and 500, and 3,000 ppm respectively. Ultrastructural elemental studies are currently in progress to determine the precise distribution of elements within single neurons.

Dr. Garruto concluded that evidence from the elemental studies coupled with the lack of a primary genetic defect in either ALS or PD, and the rapid disappearance of both disorders from Guam suggests that calcium may play a major role in the etiology of ALS and PD. The dramatic decline in incidence has occurred during the aggressive acculturation from a previously traditional horticultural and fisher-

fold subsistence economy immediately following World War II to what is presently an almost completely westernized culture with a cash economy. As a consequence of increased acculturation over the past 30 years, with a concomitant decrease in isolation, changes in dietary habits and local water supplies, and much less dependence on locally grown foodstuffs, the high incidence rates of both ALS and PD on Guam have virtually disappeared. Similar declines are evident on the Kii peninsula in Japan and, more recently, in two villages in west New Guinea where Western contact and introduction of new foodstuffs has also occurred.

5) "Aspartame; Unresolved Issues," was presented by Reuben Matalon, M.D., Ph.D., professor of pediatrics, University of Illinois at Chicago, Health Sciences Center, at the March 7, 1985, NCC meeting. A summary of his presentation is given below.

Aspartame is a synthetic compound 180-200 times sweeter than sugar consisting of two amino acids, phenylalanine and aspartic acid, held in a chemical bond by methanol. In 1981, the Food and Drug Administration approved its use as a food additive in its granular form, otherwise known as Equal, as a substitute for saccharin, and in 1983 as a sweetener in carbonated beverages, known as NutraSweet®. Since its introduction for consumption by the general population, aspartame (L-asparty1-L-phenylalanine-alphamethyl ester) has been reportedly associated with possible health hazards. Such hazards may become even more serious if aspartame's long-term use is shown to affect the activity of phenylalanine hydroxylase. To date, the following side-effects have been reportedly associated with aspartame use, i.e., menstrual difficulties, loss of memory, severe depression, visual and speech disturbances, severe headaches, seizures, and aggessive behavior in children.

Investigators looking at the possible complications with widespread aspartame use fear that when the phenylalanine found in aspartame is consumed especially with carbohydrates, changes in brain chemistry could result which would explain the aforementioned complaints. The additional load of phenylalanine from aspartame may be diverted to other metabolites such as phenylethylamine and other aromatic acids of phenylalanine. Changes in brain chemistry have been reported to result in rats given aspartame, i.e., the production of serotonin is reduced and the craving for sweetness increases.

Individuals with phenylketonuria (PKU), or carriers for PKU, are the most vulnerable to the effects of aspartame. About 20 million Americans have a genetic intolerance for phenylalanine, i.e., they lack one of the paired genes which control phenylalanine metabolism. When both parents have the same genetic intolerance for phenylalanine, one offspring in four will have the PKU condition. Females unaware of their PKU carrier state are particularly vulnerable since increases in blood levels of phenylalanine and its metabolites during pregnancy may result in their transmittal across the placenta, thereby, causing problems to the fetus. Depending on the amount of phenylalanine consumed and the stage of fetal development, developmental delays or mental retardation could result in the offspring.

The effects of aspartame are also of concern in young children, specifically carriers for PKU, since an increase in the levels of phenylalanine metabolites may lead to behavior problems and learning disabilities.

Studies are needed on the long-term effects of aspartame intake on levels of phenylethylamine, the aromatic acids of phenylalanine and tyrosine, and the effects on in vivo activity of phenylalanine hydroxylase in normal individuals, obligate carriers for PKU and patients with benign hyperphenylalaninemia. Other areas of research interest are the absorption and transport across the blood liver barrier of phenylalanine and aspartic acid, and their interaction with other amino acids including tryptophan, the branched chain amino acids, and glutamic acids.

Dr. Matalon concluded that his studies are examining the effects of consuming 100 mg/kg/day of aspartame for 12 weeks on blood and urinary metabolites of phenylalanine in normal individuals, PKU carriers, and individuals with benign hyperphenylalaninemia. The metabolites understudy include phenylalanine and other amino acids in blood and urine, and the organic acids of phenylalanine and phenylethylamine, the latter of which are potentially neurotoxic. These metabolites have not been studied with aspartame intake. The results of this research will provide insight as to whether PKU carriers differ from normal individuals in metabolizing aspartame.

6) "Childhood Obesity" was presented by William H. Dietz, M.D., Ph.D., director of clinical nutrition, division of pediatric gastroenterology and nutrition, Tufts New England Medical Center, at the April 25, 1985, NCC meeting. A summary of his presentation is given below.

Childhood obesity is an increasingly prevalent problem among children and adolescents in the United States. Upon comparing the data on childhood obesity collected over the past 15 to 20 years as part of the National Health and Nutrition Examination Surveys, it appears that the prevalence of obesity has increased by 55 percent in 6- to 11-year-old children and by 40 percent in 12- to 17-year-old children. And, obesity appears to be even more of a problem in certain groups of children; the prevalence has increased almost twice as much in preadolescent blacks as it has in preadolescent whites. Obesity is considered the major cause of pediatric hypertension and accounts for more than one-fourth of all maturity-onset diabetes mellitus.

The two measures most often used in the diagnosis of obesity are either a triceps skinfold thickness in excess of the 85th percentile, or weight for height greater than 120 percent of the desirable value, controlled for age and sex. However, the severity of obesity is probably better classified by weight for height or weight relative to the 50th percentile, since skinfold thickness is poorly correlated with total body fat among the obese.

The natural history of obesity is principally determined by its severity and age of onset. The earlier the onset of obesity in childhood, the greater the likelihood of spontaneous resolution with age. One-third of obese adults were obese during childhood, whereas approximately 80 percent of obese adolescents become obese adults. And, of those adults in excess of 160 percent of desirable body weight, more than one-half were obese as children. Thus, childhood obesity may account for a disproportionate share of severe obesity in adulthood; and the greater the severity of obesity during childhood, the more likely it will persist in adulthood.

The causes of obesity remain obscure, since consideration of potential differences in energy metabolism frequently fails to distinguish "cause" from "susceptibility" to obesity; i.e., environmental determinants are often neglected. Although an imbalance between energy intake and energy expenditure clearly exists in those who become obese, differences in total daily energy expenditure in obese individuals have not yet been reproducibly demonstrated. For example, energy intake and the proportion of calories from fat and carbohydrate do not appear to differ significantly in obese and nonobese adolescents. And, although obese adolescents appear to be less active, energy expenditure measured directly appears comparable; more work is probably needed to move the larger mass. In addition, basal metabolic rates (BMR) in obese children, adolescents and adults are comparable to, or greater than, those in the nonobese. An increase in BMR could be due to an increased lean body mass in the obese, a frequent finding in obesity of childhood onset.

If alterations in energy metabolism exist in obese individuals, they probably account for differences in "susceptibility" toward obesity rather than "cause" of obesity. The epidemiology of obesity suggests that its causes are environmental rather than physiological; i.e., those environmental factors that promote energy intake in excess of expenditure, or otherwise impair the regulation of energy balance. In studies on the association of childhood obesity with multiple variables within the physical and family environment, family variables appear to be the most important correlates of obesity. Parent-child correlations of fatness measured by skinfold thickness approximate r=0.25, irrespective of the sex of the parent or child. The risk of obesity among children increases in proportion to parental obesity. In families in which one parent is obese this risk is comparable regardless of the sex of the parent or child; obesity is not a consequence of mothering. And, if one child in the family is obese, the chance of an obese sibling is 40-80 percent.

The associations between environmental variables and obesity are not readily explained by genetic or metabolic factors. Television viewing is one environmental variable that appears to affect energy balance and metabolism, and to be directly associated with the prevalence of obesity in children and adolescents. Children who watch more than 5 hours of television a day are twice as likely to be obese as those who watch an hour or less. The most profound effects of watching television appear to be in the 12- to 17-year-old group; the number of obese children in this group increased by 2 percent for

every hour of television viewing. Approximately 10 percent who watched an hour or less per day were obese, as compared with about 20 percent of adolescents who watched more than 5 hours per day.

The metabolic implications for obesity associated with television viewing are that watching television requires no energy in excess of resting metabolic rates, and it may reduce the time spent in more energy-expensive activities. Also, television advertising of junk food may contribute to obesity of young viewers; most stars who advertise these foods are slim and trim, implying that consumption of these foods does not influence weight. Thus, it appears that the prevalence of obesity could be reduced by a reduction in television viewing and an increase in other activities. Additional mechanisms that link physical and family environmental variables with obesity have not yet been defined.

A variety of therapies are available for the treatment of obesity. The goals of optimal hypocaloric dietary therapy are to minimize alterations in protein metabolism, to maximize fat losses, and to enhance dietary adherence. The principle factors that affect protein metabolism appear to be the levels of protein and energy intake. Although there is little dispute that protein is more protein sparing than either carbohydrate or fat, the protein-sparing effects of additional energy supplied as protein, carbohydrate or fat are still debatable. Furthermore, the comparative effects of different diets on fat losses require further investigation.

In tests of compliance to various weight reduction regimens, obese adolescents given hypocaloric diets of varying composition, i.e., with or without carbohydrate, have shown comparable success rates in weight loss. This suggests that compliance is not related to diet per se. Adherence to weight reduction regimens in children and adolescents appeared to be related more to family dynamics; reproducible patterns of family interaction appear to exist within certain subgroups of patients. For example, in a study of obese adolescent girls with one obese parent, this parent appeared over-involved with the obese daughter, such that the daughter felt that losing weight would be an act of disloyalty to the obese parent, and remaining obese would be disloyal to the nonobese parent. Such patterns of family interaction influence the potential for weight reduction, and may neutralize the therapeutic intervention proposed by the practitioner.

Dr. Dietz concluded that some data suggest that a broad, family-oriented approach to weight reduction may improve the outcome of therapy, since it offers the following advantages: 1) The entire family becomes responsible for the obese child, as well as for successful weight reduction. This reduces the blame directed at the obese child and, with it, the addition of another failure to a self-image already impaired. 2) A variety of family behaviors related to food intake which are not generally considered in individually-oriented therapy, are incorporated into the therapy. 3) A family-oriented therapeutic approach offers new and testable hypotheses, thereby increasing the number of strategies effecting compliance.

Behavior modification directed at altering eating behavior continues to play an important role in weight reduction of children and adolescents. However, such strategies are usually ineffective in families where parents are not consistently supportive, and when conflict exists regarding the parent's weight. Nonetheless, the prevalence of obesity and the implications of childhood obesity for severe adult disease emphasize the need for effective programs directed at the prevention of obesity in children.

7) "Incidence and Precursors of Hypertension In Young Adults," was presented by Mr. Robert Garrison, chief, Field Studies and Biometry Branch, of Epidemiology and Biometry Program, DECA, NHLBI, at the June 6, 1985 NCC meeting. A summary of his presentation is given below.

A prospective study to examine the occurrence of hypertension and its precursors was carried out on the adult offspring of the Framingham study cohort. The participants included 2,027 men and 2,267 women who were first enrolled for physical examinations and interviews in 1971-1975. These subjects were followed for 8 years at which time they were invited for a second examination. The criteria for hypertension were based on the reported use of prescription drugs and on the two systolic blood pressure (SBP) and fifth phase diastolic blood pressure (DBP) measures to the nearest 2 mm Hg. A participant was considered hypertensive if the physician determined that the patient was currently taking medication specificially prescribed to lower his blood pressure, or either of the two SBP measurements was $\geq$ 160 mm Hg and either of the two DBP measurements $\geq$ 95 mm Hg. Lipoprotein cholesterol and triglyceride measures were also taken.

In order to better understand the factors that predispose individuals to the development of hypertension, attributes measured at the first examination were evaluated for their association with hypertension incidence. The attributes examined included those related to SBP or DBP at the first examination, in addition to subscapular skinfold thickness (SSF). Both age-specific and age-controlled univariable logistic analysis demonstrated that SSF was consistently and strongly associated with the development of hypertension in the eight years following the first examination. The most prominent finding was the strength of this association in all groups but the youngest group of men. For example, extremely obese women in their fourth decade were nearly seven times more likely to develop hypertension than were lean women of the same age.

Baseline blood pressure measured at the first examination appeared to be the best single predictor of hypertension incidence. However, in terms of potentially modifiable attributes associated with the development of hypertension, and therefore possibly in the causal pathway to hypertension pathology, body fat appeared to be the prominent precursor to hypertension. Furthermore, hypertension was shown to more likely develop in obese subjects, regardless of their initial blood pressure. In order to further document the importance of body fat levels as a major determinant of blood pressure, a second SSF

measurement, obtained at the second examination, was used in a multivariate regression model that related the change in SSF to the change in SBP and DBP, after controlling for baseline blood pressure and SSF. These analyses confirmed that body fat changes that occurred in the eight year interval between examinations showed statistically significant positive associations with both SBP and DBP changes in both men and women.

The nature of the mechanisms underlying this association remain conjectural; abnormalities in cell membrane cation transport, which result in an increase of intracellular sodium, have been demonstrated both in obesity and hypertension. Hyperinsulinemia may also play a role in obesity-related hypertension, operating through insulin-induced enhancement of renal sodium reabsorption and greater sodium retention.

The results of this research indicate that blood pressure tends to increase as people gain weight, and that blood pressure usually falls commensurate with weight reduction. This examination of the obesity-hypertension relationship did not take into account the body distribution of adiposity, and evidence does exist that only central obesity is related to hypertension. If this relationship is true, the findings in this study are likely to underestimate the obesity-hypertension relationship.

Mr. Garrison concluded that the relationship between body fat and hypertension may be stronger than was previously thought in young or middle-aged adult subjects. The majority of hypertension in women and much of the early-onset hypertension in men can be attributed to excess body fat. Thus, these findings emphasize the need for body fat assessment, not only as an epidemiological tool to better understand cardiovascular disease pathology, but as a tool for the physician to better assess his patient's long-term morbidity outlook. Finally, these results suggest that aggressive weight reduction and/or obesity prevention could have substantial impact on the burdensome load of hypertension in middle-aged adults.

8) A special joint seminar entitled "A Calorie is A Calorie?? Efficiency of Energy Utilization," was held at the July 11, 1985, NCC meeting. The seminar included a presentation on "Dietary Fat and Neoplasia--The Role of Net Energy on Enhancement of Carcinogenesis: Effects of Fat and Calories on Immune Functions" by Michael Pariza, Ph.D., chairman, department of food microbiology and toxicology, University of Wisconsin, and a presentation on "Dietary Fat, Carbohydrate Balance and Weight Maintenance" by Jean-Pierre Flatt, Ph.D., professor of biochemistry, University of Massachusetts Medical Center. The summary of these presentations are given below.

"Dietary Fat and Neoplasia--The Role of Net Energy on Enhancement of Carcinogenesis: Effects of Fat and Calories on Immune Functions" by Michael Pariza, Ph.D.

The modulating effects of dietary fat and caloric restriction on carcinogenesis in rodents are well documented. Early studies sug-

gested that the net energy value of a high-fat diet could account for the enhancing effect on carcinogenesis. Several investigators have shown that as the amount of fat in the diet increases, the amount of energy expended by the animal as heat decreases, and thus, more energy is retained in the carcass of the animal. This increased efficiency of energy utilization from fat may explain the enhancement of epidermal carcinogenesis in mice fed a high-fat diet.

To further investigate this phenomenon, female Fisher F344 rats +reated with DMBA (7,12-dimethylbenz(a)anthracene) to initiate breast carcinogenesis were fed refined diets containing 5 percent corn oil (low fat) or 30 percent corn oil (high fat). The concentrations of protein, vitamins, minerals and fiber in both diets were balanced to account for differences in caloric density. Following initiation with DMBA, at 52 days of age the animals were divided into three groups: the first group was given free access to the high fat diet; the second group free access to the low fat diet; and the third group was given the high-fat diet, but, in amounts restricted, in terms of net energy, to that consumed by the rats fed the low-fat diet. At 24 weeks, the tumor incidence among these groups was, respectively, 73 percent, 43 percent and 7 percent, despite the fact that the third group was consuming more than three times as much fat as the second group. Moreover, while the first group was heavier, the weights of the second and third groups were not significantly different, indicating that the restriction placed on the third group did not result in growth retardation. Analysis of body composition established that the rats fed the high fat diets (ad lib or restricted) contained 60 percent more body fat than the rats fed the low-fat diets. These observations are consistent with the assumption that the high fat diet was utilized more efficiently, and therefore supplied more net energy.

Dr. Pariza concluded that the data indicate that rats can consume a high-fat diet (providing 60 percent of the calories as fat, and a total quantity of 2.2 grams of fat/day), and yet develop fewer tumors than rats fed a low fat diet (providing only 10 percent of the calories as fat and a total quantity of 0.6 grams of fat /day). Thus, these data support the hypothesis that the "net energy" intake, rather than the kilocalories of intake or the percent fat in the diet, is central in the enhancement of mammary carcinogenesis.

"Dietary Fat, Carbohydrate Balance and Weight Maintenance" by Jean-Pierre Flatt, Ph.D.

Weight maintenance requires not only equivalence between energy intake and energy expenditure, but also adjustment of the composition of the fuel mix oxidized to the nutrient distribution in the diet. The need to simultaneously satisfy these conditions creates constraints that are not apparent when considering merely the overall balance between energy intake and energy expenditure. Thus, individuals are driven towards the particular state in which their glycogen reserves, and their protein and adipose tissue masses are such as to cause the relative contributions of glucose, amino acids and fatty acids in the fuel mix oxidized to equal the nutrient distribution in

the diet. The particular body composition that corresponds to this steady state is then defended, as long as lifestyle and dietary habits remain constant, explaining a behavior sometimes rationalized by postulating the existence of a ponderostat.

Energy expenditure and substrate oxidation rates are commonly determined by measuring the oxygen consumption, CO_2 production and urinary nitrogen excretion (i.e., "indirect calorimetry") since there is a precise relationship between heat release, liters of oxygen consumed, and respiratory quotient (RQ). RQ is the ratio of CO_2 formed to O_2 utilized. Similarly, the ratio of CO_2 formed to O_2 utilized during the combustion of a representative sample of the dietary nutrient mixture can be called the food quotient (FQ). Since protein contributes only a minor fraction of the metabolic energy and the RQ for protein oxidation is 0.80, the RQ and the FQ are determined primarily by the carbohydrate-to-fat ratio. By comparing the RQ to the FQ, one can assess to what extent the fuel mixture oxidized by the body differs from the fuel mixture in the diet.

For a constant body composition to be maintained, the average RQ must be equal to the FQ. Periods with the RQ below the FQ must offset periods with the RQ above the FQ. Because the RQ after an overnight fast (=0.82) is barely below the FQ (=0.85) for a typical mixed diet supplying 40 percent of the calories as fat, it may be difficult for the organism to operate at an average daily RQ as low as the FQ in the absence of physical activities which favor a decrease in RQ. If, for instance, the fuel mixture oxidized during the day has an average RQ higher than 0.85, the mixture contains a higher proportion of carbohydrate than the typical mixed diet. In order to recover the oxidized carbohydrate, food would have to be consumed in amounts exceeding the energy expenditure, which is possible by storing a portion of the ingested fat. In time, accumulation of fat increases the adipose tissue mass, leading to higher free fatty acid levels and sometimes creating insulin resistance, while promoting the use of fatty acids relative to glucose. On diets with a relatively high fat content (such as the mixed diets consumed in affluent societies) a substantial expansion of the adipose tissue mass appears to be often necessary before the use of fat as a fuel becomes commensurate with the diet's fat content. This is particularly likely when the constant availability of highly palatable foods acts to prevent a sufficient reduction in the range within which glycogen levels tend to be spontaneously maintained.

The exchange of fat for carbohydrate in the diet can have a marked effect on body composition and body weight because the storage capacities for glycogen and fat differ by two orders of magnitude. Indeed, this tremendous difference has major implications on the metabolic responses to dietary carbohydrate and dietary fat, given the physiological importance of blood glucose homeostasis. Thus, biological evolution had to foster the development of metabolic, endocrine and behavioral mechanisms that give a greater priority to the maintenance of carbohydrate than to the preservation of fat or of overall energy balance. Studies on the metabolic responses to carbohydrate and fat intake in man, as well as measurements of daily

variations in the carbohydrate and fat balances among ad-libitum-fed mice, support this contention and the view that the regulation of food intake may be geared primarily toward the maintenance of carbohydrate balance, rather than overall energy balance.

Dr. Flatt drew attention to the importance of the composition of expended energy in relation to the composition of the diet. The concept that the average RQ must equal to the FQ of the diet consumed suggests that weight maintenance is facilitated by including physical activities in the daily routine, selected for their effect in lowering the RQ, and by reducing the fat content of the diet in order to elevate the FQ. A strategy for weight maintenance is envisaged whose goal is to ensure that fat oxidation is at least as great as fat intake. This provides a more specific objective than recommendations aiming at achieving energy balance by limiting intake and increasing expenditure.

Recognition of the different effects of dietary fat and carbohydrate on metabolism, and of their particular leverages in influencing steady-state body composition, may help to explain the increased incidence of obesity among people and animals consuming diets with a relatively high fat content.

9) "Dietary Fat and Female Sex Hormones" was presented by Sherwood L. Gorbach, M.D., professor of medicine, Tufts New England Medical Center Hospital at the September 5, 1985, NCC meeting. A summary of his presentation is given below.

The evidence that nutritional status and diet can influence the production and excretion of estrogen hormones in women has been accumulating from a number of epidemiological studies, particularly those of breast cancer. Some studies have correlated dietary fat intake with breast cancer risk, an association that has also been established in experimental animal models. Other studies have linked sex hormones, most notably estrogens, with breast cancer risk. Higher plasma and urine levels of estrogens are thought to be related to human breast cancer.

In Western countries women consume diets that are high in fat and animal protein and low in dietary fiber, whereas women in developing countries consume vegetarian or semivegetarian diets that have the opposite characteristics. Intake of animal fat is positively correlated with the incidence of breast cancer in several countries; and, among women who migrate from low-risk to high-risk areas, differences in breast cancer incidence remain stable, provided that they continue to eat their customary diets.

A number of studies have been conducted to examine the possible relationship between dietary intake, estrogen metabolism and risk for breast cancer. One study was conducted to describe the patterns of estrogen excretion among premenopausal American white women who were either vegetarians or omnivores, controlling for body weight, reproductive history, ingestion of certain drugs, and various diseases. The vegetarian and omnivorous participants did not differ signifi-

cantly in their mean ages, heights, or weights. Their mean intakes of calories and protein were similar, although the omnivores consumed 43 percent of their protein from nonvegetable sources, while the vegetarians consumed only 7 percent from nonvegetable sources--from fish. The omnivores consumed 12 grams of fiber per day, and significantly more total fat (40 percent of total calories) and saturated fat per 1,000 kcal of food intake. The vegetarians consumed significantly more fiber, at 28 grams per day, and 30 percent of their calories from fat.

The mean fecal excretion of estrone, estradiol, estriol, and total estrogen among the vegetarian women was twofold to threefold higher per 24 hours than among omnivores. Compared with the omnivores, the vegetarians also had significantly less urinary excretion of estriol--the estrogen reported to have the greatest enterohepatic circulation; 15 percent lower plasma levels of estrone; 19 percent lower plasma levels of estradiol; similar levels of testosterone; 11 percent higher plasma levels of androstenedione; and excreted more than twice as much feces (wet or dry weight). A positive correlation was shown between individual fecal weight and fecal excretion of estrogen, suggesting that group differences in fecal excretion of estrogen may have been due to fecal bulk.

In both dietary groups, the differences in plasma and fecal levels of estrogen were associated with changes in daily fecal output. The combined fecal and urinary estrogen excretion (total excretion) was only slightly higher in the vegetarians than in the omnivores, suggesting that the increased fecal loss in vegetarians was nearly balanced by their decreased urinary excretion. In addition, the level of urinary estriol-3-glucuronide, which is formed almost exclusively in the intestinal mucosal cells at the time of reabsorption of biliary estriol, was lower in the urine of the vegetarians. This finding, along with the negative correlation observed between levels of urinary estriol-3-glucuronide and fecal estriol, suggests a decreased level of estrogen in the enterohepatic circulation of vegetarians. The significant inverse relationship between levels of estrogen in the plasma and in excreted feces suggests that the decreased level of estrogen in the enterohepatic circulation affects the level of circulating plasma estrogen.

The dietary factor responsible for the alteration in fecal excretion of estrogen is not known. Fat and fiber are thought to be involved because of their effects on bile flow and fecal bulk, respectively. In this study, vegetarians consumed fewer calories as fat and more fiber than did the omnivores. However, the vegetarians also consumed less animal protein and all factors associated with it (saturated fat, cholesterol, etc.).

Another study included 12 premenopausal Asian women recently migrated to Hawaii, 9 postmenopausal Oriental immigrants living in Hawaii, and 10 premenopausal and 11 postmenopausal omnivorous Caucasian women living in Boston. The Caucasian women ate diets that were higher in animal foods and different in other food choices than those of the Oriental women. They consumed 38-40 percent of total calories as

fat, while the Oriental women consumed significantly less calories and total fat (19-22 percent of total calories). The postmenopausal Orientals also had a significantly lower protein intake than the Caucasian women, while both age groups of Oriental women had a greater percentage of calories coming from carbohydrate. Among Caucasians, fiber intake was approximately 20 percent lower and the fat-to-fiber ratio was significantly higher than in the Oriental women.

The premenopausal Oriental women had excreted in the feces approximately two times more estrone, three times more estradiol, four times more estriol, and three times more total fecal estrogen excretion per 24 hours than did the premenopausal Caucasians. Pre- and postmenopausal Oriental women excreted in the urine significantly less estrone, estradiol, and total estrogen (sum of the three principal estrogens) per 24 hours than did their age-matched Caucasian peers. The postmenopausal Orientals also excreted less estriol compared with postmenopausal Caucasians, however, there was no difference in urinary estriol excretion between the younger Orientals and Caucasians. Premenopausal Oriental women had significantly lower plasma levels of estrone, estradiol, testosterone, and androstenedione than their Caucasian peers. The postmenopausal Oriental women also had lower plasma estrogen and androgen levels compared with the older Caucasian women.

Total dietary fat intake was positively correlated with plasma estradiol and estrone for the premenopausal women. The within-group analysis of total fat intake versus the concentration of plasma estradiol showed a positive correlation for the Orientals and Caucasians. Further analysis of data from the combined groups showed a correlation between saturated fat intake and plasma estrone levels, while no correlation was observed between the intake of polyunsaturated fat and plasma estrone or estradiol. These findings indicate that the correlation between plasma estrogen and dietary fat is caused primarily by the amount of saturated fat in the diet. An inverse correlation between dietary fiber intake and plasma estrone and plasma estradiol was also observed among the premenopausal women of both groups.

A number of mechanisms have been proposed to explain the effects of diet on estrogen metabolism. 1) Diet can affect the synthesis or the clearance rate of estrogens--an increased clearance rate among vegetarians or low fat consumers could account for lower plasma and higher urinary levels of estrogens. 2) Diet can alter the conversion of androgens to estrone and estradiol. This aromatization can occur in adipose tissue, a major source of estrogens in postmenopausal women which may be particularly sensitive to dietary changes. 3) The association of a vegetarian or a low fat diet with lower plasma and urinary estrogen concentrations might be due to a metabolic shift that increases the conversion to 2-hydroxy catechol estrogens--a shift from 16-hydroxylation to 2-hydroxylation would also result in lower estriol levels and higher amounts of 2-hydroxyestradiol. 4) Diet may alter the enterohepatic circulation of estrogens by altering the reabsorption of estrogen from the intestine, thus, the

lower plasma estrogen concentration may result from decreased enterohepatic circulation. A possible explanations for the reduced enterohepatic circulation of estrogen in vegetarian women is their high consumption of dietary fiber, which accounted for the higher fecal weight. The greater fecal bulk and nonabsorbed fiber may somehow "shield" the estrogens excreted in the bile from deconjugation and reabsorption. A high fiber diet exerts a clathric, or trapping, effect of estrogens in the bowel lumen. Also, a vegetarian diet or a low fat/high fiber diet may decrease the ability of the intestinal flora to deconjugate biliary estrogen conjugates, a necessary step for their reabsorption. Since estrogens are excreted in the bile as glucuronide and sulfate conjugates, vegetarians might hydrolyze fewer estrogen conjugates, resulting in lower intestinal reabsorption and greater fecal excretion of estrogens. The reduced b-glucuronidase activity in the feces of vegetarians supports this hypothesis.

Dr. Gorbach concluded that the Oriental women who immigrated to the U.S. but who continued to consume diets similar to those consumed in Southeast Asia had lower serum and urinary estrogens, and higher fecal estrogens than North American omnivores. Consumption of saturated fat appeared to influence plasma estrogens more than polyunsaturated fats; however, the correlation between total dietary fat and estrogens is even stronger suggesting that the quantity of dietary fat may also play a role. The influence of dietary fiber cannot be separated from that of dietary fat, because a high fiber diet tends to be associated with a low fat diet and vice versa.

Current studies with premenopausal omnivore women put on a low fat diet (20 percent of the calories from fat) confirm the findings that diet affects the enterohepatic system and estrogen levels. After 2 months on the low fat diet, the serum levels of estrone sulfate show a significant decline. Radiolabelled studies demonstrate decreased urinary excretion of an important metabolite 16-a-OH-estrone, as well as other estrogens. These studies reaffirm the relationship between diet and estrogen metabolism, and therefore may provide some guidance for dietary recommendations.

APPENDIX E

LEGISLATIVE AUTHORITY OF NIH FOR HUMAN NUTRITION

LEGISLATIVE AUTHORITY OF NIH FOR HUMAN NUTRITION RESEARCH

In November 20, 1985, the Health Research Extension Act of 1985 became Public Law 99-158. This act amended the Public Health Service Act "To revise and extend the authorities under that Act relating to the National Institutes of Health and for other purposes." The law reorganized the NIH by dividing the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases (NIADDK) into two new Institutes--the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). The law also established the National Center for Nursing Research.

Four Institutes have specific mandates to conduct nutrition research at the NIH. Those mandates are as follows:

NCI: Section 413(a)--"establish an information and education center to collect, identify, analyze, and disseminate on a timely basis, through publications and other appropriate means, to cancer patients and their families, physicians and other health professionals, and the general public, information on cancer research, diagnosis, prevention, and treatment (including information respecting nutrition programs for cancer patients and the relationship between nutrition and cancer)..."

NHLBI: Section 420(1)--"dissemination of information regarding diet and nutrition, environmental pollutants, exercise, stress, hypertension, cigarette smoking, weight control, and other factors affecting the prevention of arteriosclerosis and other cardiovascular diseases and of pulmonary and blood diseases; and (2) the dissemination of information designed to encourage children to adopt healthful habits respecting the risk factors related to the prevention of such diseases..."

Section 421(a)(1)(A)--"investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases;..."

NIDDK: Section 426--"conduct and support of research, training, health information dissemination, and other programs with respect to diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and kidney, urologic, and hematologic diseases..."

Section 428(a)(1)--"In the Institute there shall be a Division Director for Diabetes, Endocrinology, and Metabolic Diseases, a Division Director for Digestive Diseases and

Nutrition...responsible for--(A) developing a coordinated plan (including recommendations for expenditures) for each of the national research institutes within the National Institutes of Health with respect to research and training concerning diabetes, endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases; (B) assessing the adequacy of management approaches for the activities within such institutes concerning such diseases and nutrition and developing improved approaches if needed; (C) monitoring and reviewing expenditures by such institutes concerning such diseases and nutrition; and (D) identifying research opportunities concerning such diseases and nutrition and recommending ways to utilize such opportunities...(b)(1) carry out programs of support for research and training (other than training for which National Research Service Awards may be made under section 487) in the diagnosis, prevention, and treatment of diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and...(2) establish programs of evaluation, planning, and dissemination of knowledge related to such research and training."

Section 432--"There are established within the advisory council for the Institute appointed under section 406 a subcommittee on diabetes and endocrine and metabolic diseases, a subcommittee on digestive diseases and nutrition, and a subcommittee on kidney, urologic, and hematologic diseases...The subcommittees are authorized to review applications made to the Director of the Institute for grants for research and training projects relating to the diagnosis, prevention, and treatment of the diseases for which the subcommittees are established and shall recommend to the advisory council those applications and contracts that the subcommittees determine will best carry out the purposes of the Institute. The subcommittees shall also review and evaluate the diabetes and endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases programs of the Institute and recommend to the advisory council such changes in the administration of such programs as the subcommittees determine are necessary."

NIAMS: Section 440(6)--"...projects for investigation into the epidemiology of all forms and aspects of arthritis and musculoskeletal diseases, including investigations into the social, environmental, behavioral, nutritional, and genetic determinants and influences involved in the epidemiology of arthritis and musculoskeletal diseases..."

Other Institutes that conduct and support nutrition research do so under much broader authority. Each conducts research programs in the "diagnosis, prevention, and treatment" of specific diseases and life processes within their areas of responsibility. These authorities are as follows:

NIDR	Section 453
NINCDS	Section 457
NIGMS	Section 461
NICHD	Section 448
NEI	Section 455
NIEHS	Section 463
NIA	Section 444
DRR	Section 480 (Supporting research resources)
International Cooperation Authority	Section 482
Training Authority	Section 487

NOTES:

NIDDK (Section 427), has established two clearinghouses, namely the National Digestive Diseases and Nutrition Clearinghouse and the National Kidney and Urologic Diseases Information Clearinghouse and NIAMS (Section 438) (b) has established the National Arthritis and Musculoskeletal and Skin Diseases Clearinghouse to facilitate and enhance the distribution of information regarding these specific disease areas to health professionals, patients, and the public. Nutrition information is often included.

In order to place more emphasis on research on health maintenance and disease prevention the Health Research Extension Act of 1985 established the appointment of an Associate Director for Disease Prevention within the NIH Office of the Director, the NCI, and NICHD. A similar position has existed at NHLBI by current law. The associate directors are to "assure that each institute's research plans include sections dealing with such prevention related research as investigations into the epidemiology of disease; studies of the etiology of diseases (including the effect of diet and other personal habits on the development of disease, and the effect of environmental factors, including air, water, radiation, and toxic substances, on the development of disease); research into immunizations against disease; studies of the means to preclude the development of disease through changes in personal habits and environmental factors; and studies of methods for, and the cost-effectiveness of, population screening programs" The Associate Director of Prevention within the Office of the Director, NIH, is responsible for promoting and coordination of the research programs of all Institutes regarding the prevention of disease.

*U.S. G.P.O. 1987-181-296:41277

DISCRIMINATION PROHIBITED: Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors or subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the Nutrition Coordinating Committee must be operated in compliance with these [illegible] Executive Orders.

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